Cholecystokinin Antagonists: Pharmacological and Therapeutic Potential

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Abstract: Cholecystokinin (CCK) is a regulatory peptide hormone, predominantly found in the gastrointestinal tract, and a neurotransmitter present throughout the nervous system. In the gastrointestinal system CCK regulates motility, pancreatic enzyme secretion, gastric emptying, and gastric acid secretion. In the nervous system CCK is involved in anxiogenesis, satiety, nociception, and memory and learning processes. Moreover, CCK interacts with other neurotransmitters in some areas of the CNS. The biological effects of CCK are mediated by two specific G protein coupled receptor subtypes, termed CCK_1 and CCK_2. Over the past fifteen years the search of CCK receptor ligands has evolved from the initial CCK structure derived peptides towards peptidomimetic or non-peptide agonists and antagonists with improved pharmacokinetic profile. This research has provided a broad assortment of potent and selective CCK_1 and CCK_2 antagonists of diverse chemical structure. These antagonists have been discovered through optimization programs of lead compounds which were designed based on the structures of the C-terminal tetrapeptide, CCK-4, or the non-peptide natural compound, asperlicin, or derived from random screening programs. This review covers the main pharmacological and therapeutic aspects of these CCK_1 and CCK_2 antagonist. CCK_1 antagonists might have therapeutic potential for the treatment of pancreatic disorders and as prokinetics for the treatment of gastroesophageal reflux disease, bowel disorders, and gastroparesis. On the other hand, CCK_2 antagonists might have application for the treatment of gastric acid secretion and anxiety disorders. © 2003 Wiley Periodicals, Inc. Med Res Rev, 23, No. 5, 559–605, 2003

Key words: colecystokinin; CCK_1 receptors; CCK_2 receptors; antagonists

1. INTRODUCTION

Cholecystokinin (CCK) was first discovered in 1928 as a hormone in the gastrointestinal tract,[1] which was identified in 1966 as a 33 amino acid peptide in porcine intestine extracts, and it was originally

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named cholecystokinin-pancreozymin.[2,3] Later, CCK was found in the central nervous system (CNS),[4–7] and it is now generally believed to be the most widespread and abundant neuropeptide in the CNS. In the gastrointestinal tract CCK is released from endocrine cells in response to food intake, and regulates motility, contraction of gall bladder, pancreatic enzyme secretion, gastric emptying, and gastric acid secretion.[8] In the nervous system CCK is involved in anxiogenesis,[8–11] satiety,[8,12–14] nociception,[8,15] thermoregulation,[8,16] and memory and learning processes.[9,17,18] Furthermore, the colocalization and interaction of CCK with other neurotransmitters in some CNS areas,[8,19] mainly with dopamine (DA),[20,21] suggests its implication in several neuropsychiatric disorders, such as schizophrenia, depression, and drug addiction.[20–24]

Besides the 33-amino acid sequence, CCK-33, formerly isolated and identified in porcine intestine, other species-specific molecular forms of CCK, derived from a 115-amino acid precursor protein (prepro-CCK[25]), have been characterized later, such as CCK-58, CCK-39, CCK-22, CCK-8 [Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2], unsulfated CCK-8, CCK-7, unsulfated CCK-7, CCK-5, and CCK-4 (Trp-Met-Asp-Phe-NH_2), which have in common the C-terminal sequence[8,26] (Fig. 1). In humans CCK-58 and CCK-8 are the major forms.[27] This last octapeptide is relatively conserved across species, and appears to be the minimum sequence for full biological activity.[27]

2. CCK RECEPTORS

The biological actions of CCK are mediated by two specific G protein coupled receptor (GPCR) subtypes, initially named CCK-A (for alimentary) and CCK-B (for brain).[23,27] This nomenclature has been recently changed to CCK_1 and CCK_2, respectively, according to the guidelines of the International Union of Pharmacology (IUPHAR) Committee on Receptor Nomenclature and Drug Classification.[28] These receptors were pharmacologically classified on the basis of their affinity for the endogenous peptide CCK agonists and gastrin (Fig. 1), which share the same C-terminal pentapeptide amide sequence.

A. CCK_1 Receptors

As shown in Table I, these subtype receptors bind CCK-8 with a 500- to 1,000-fold higher affinity than gastrin or nonsulfated CCK-8, and a 10,000-fold higher affinity than CCK-4, and this binding is selectively inhibited by the antagonist devazepide (L-364,718).[27] These receptors are mainly localized in the gastrointestinal tract (pancreas, gall bladder, gastric mucosa, pyloric sphincter, sphincter of Oddi, and lower esophageal sphinter), where they are responsible of the regulation of

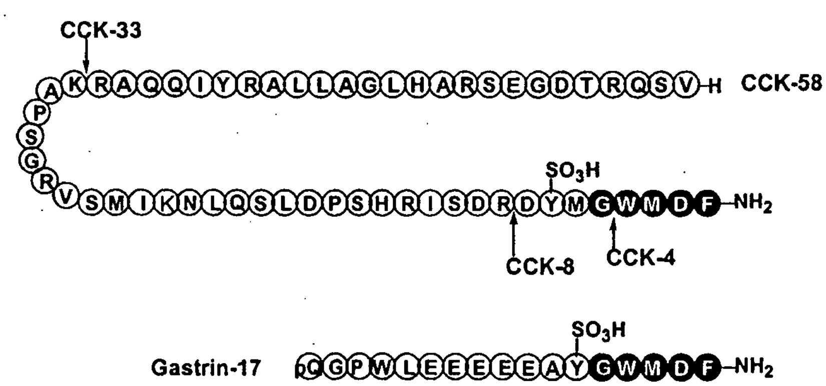


Figure 1. Amino acid sequence of the most predominant mammalian forms of CCK (CCK-58, CCK-33, CCK-8, and CCK-4, using single-letter amino acid symbols), and the major form of gastrin (gastrin-17). Filled circles show identical C-terminal pentapeptide sequence shared between CCK and gastrin. pQ, pyroglutamic acid.

Table I. Summary of Characteristics, Localization, and Functions of CCK Receptor Subtypes

IUPHAR nomenclature[a]	CCK_1	CCK_2
Initial nomenclature[a]	CCK_A	CCK_B, CCK_B/gastrin
Endogenous agonists affinity rank order[a]	CCK-8 >> gastrin, unsulfated CCK-8 (500-1000-fold) > CCK-4 (10-fold)	CCK-8 > gastrin, unsulfated CCK-8 (0-10) > CCK-4 (60-fold)
Main selective antagonists in rank order of affinity (pKi)[a]	Devazepide (9.8), T-0632 (9.6) SR-27897 (9.2), IQM-95,333 (9.2), PD-140,548 (7.9-8.6), lorglumide (7.2)	YM-022 (10.2), L-740,093 (10.0), GV-150,013 (9.3), RP-73,870 (9.3), L-365.260 (7.5-8.7), LY-26,2691 (7.5)
G Protein coupling[a]	$G_{q/11}$, G_s[1]	$G_{q/11}$
Signal transduction[b]	PLC, IP_3, DAG, Ca^{2+} PLA_2/arachidonic acid Camp	PLC, IP_3, DAG, Ca^{2+}
Gastrointestinal (GI) tract localization and functions[b]	Pancreatic acini: enzyme secretion, growth Pancreatic islets: insulin secretion Gastric mucosa: Pepsinogen release from chief cell Somatostatin release from D cells Gallbladder and GI smooth muscle: Contraction and motility	Gastric mucosa: Growth Gastric acid secretion from parietal cells Histamine release from ECL cells Pepsinogen release from chief cell Inhibition of somatostatin release in D cells
CNS and PNS localization and functions[b]	Selected areas of the CNS and vagus nerve: satiety Posterior nucleus accumbens: DA release Dorsal horn of the spinal cord: Antagonism of opiod analgesia	Throughout CNS: Anxiety, neuroprotection, memory and learning, drug addiction, Antagonism of analgesia Dopaminergic pathways: inhibition of DA release
Other localizations[b]	Tumoral cell lines: AR42J, CHP212	Immune cells: monocytes and T lynphocytes Tumoral cells: medullary thyroid, gastric and colonic carcinomas, AR42J, small cell lung carcinoma, astrocytomas, leiomyosarcoma

[a]Reference 55.
[b]References 23 and 27.

diverse digestive processes.[23,27,29] They are also present in select areas of the peripheral nervous system (vagus nerve), and the CNS [nucleus tractus solitarius (NTS), posterior nucleus accumbens, hypothalamic dorsomedial nucleus, dorsal horn of the spinal cord, and anterior pituitary corticotrophs],[23,27] where they mediate the satiety effects of CCK,[12,14] regulate an increase in dopamine release,[20,27] and antagonize opiod analgesia.[27,30,31] CCK_1 receptors have also been characterized in diverse tumoral cell lines, where they may mediate growth.[27,32,33]

The CCK_1 receptor cDNA was first cloned from rat pancreas, which showed a 429 amino acid sequence,[34] subsequently it was cloned from guinea pig gall bladder, pancreas, and gastric chief cells,[35] human gall bladder,[36,37] and rabbit stomach.[38] CCK_1 receptors are highly conserved among these species with an overall amino acid homology of 80%.[23] As above mentioned, these receptors belong to the superfamily of GPCR, whose activation starts the signal transduction cascade of phospholipase C (PLC), with the formation of the second messengers, inositol 1,4,5-triphosphate (IP_3) and 1,2-diacylglycerol (DAG), leading to the release of intracellular Ca^{2+} and the activation of protein kinase C (PKC).[23,27] Depending on the agonist used, CCK_1 receptor activation may result in

stimulation of phospholipase A_2 (PLA_2), which regulates Ca^{2+} release through the arachidonic acid cascade.[23] Moreover, it has been shown that high concentrations of CCK-8 can stimulate the adenylate cyclase signal transduction pathway with formation of 3′5′-cyclic monophosphate (cAMP)[23,27] (Table I).

B. CCK_2 Receptors

As summarized in Table I, the order of affinities for this receptor subtype is CCK-8 > gastrin or nonsulfated CCK-8 (0- to 10-fold) > CCK-4 (60-fold),[27] and the binding is selectively inhibited by the antagonist L-365,260. These receptors are mainly found throughout the CNS, where they have been proposed to be responsible of the anxiogenic,[8–11] and neuroprotective[8,39–41] effects of CCK, and of the involvement of CCK in nociception,[8,15,18] drug addiction,[18,20–24] and memory and learning processes.[18,23,27] In the dopaminergic pathways CCK_2 receptor activation inhibits dopamine release.[8,20,27] In the gastrointestinal tract, CCK_2 receptors inhibit the release of somatostatin from D cells, and mediate the contraction of smooth muscle cells, the acid secretion from parietal cells, and the release of histamine from enterochromafin-like (ECL) cells and pepsinogen from chief cells.[23,27,29] These receptors are also present on pancreatic acinar cells in dogs and guinea pig, where they mediate growth but not enzyme secretion,[27] and on immune cells such as monocytes[42] and T lymphocytes,[43] where their function is unknown. Like CCK_1, CCK_2 receptors are expressed in diverse tumors and tumor-derived cell lines such as medullary thyroid, gastric, colon, ovarian, and small cell lung carcinomas, astrocytomas, and certain pancreatic cell lines, where they elicit cellular proliferation.[23,27,44]

CCK_2 receptors have been cloned from various sources:[23] rat brain and stomach, the pancreatic tumoral cell line AR4-2J, human brain and stomach, guinea pig gall bladder and stomach, brain and gastric enterochromaffin-like and parietal cells of *Mastomys natalensis*, calf pancreas, and a rabbit genomic library. The sequencing of the cDNA of the rat CCK_2 receptor showed the presence of 452 amino acids,[45] and this receptor subtype is highly conserved in humans, canine, guinea pig, calf, rabbit, *M. Natalensis*, and rat, with an overall amino acid identity of 72%.[23] These receptors were historically viewed as distinct of gastrin receptors on the basis of their different relative affinities for CCK and gastrin like peptides.[46] However, the cloning of human, guinea pig and rat,[45,47] and canine[27] brain CCK_2 receptors resulted in a single cDNA identical to that for the canine parietal cell gastrin receptor.[48] More recently, additional CCK receptor subtypes could not be identify in the cloning of CCK_1 and CCK_2 receptors of guinea pig stomach smooth cells, by hybridization screening of a guinea pig smooth muscle cDNA library, using ^{32}P random primed labeled cDNA probes from cloned rat CCK_1 and CCK_2 receptor coding regions.[49] The previously observed differences in receptor pharmacology between CCK_2 and gastrin receptors have been attributed to tissue-specific differences in receptor processing or membrane lipids, variation in receptor preparations between tissues, and to interlaboratory variation.[27] On the other hand, studies on several tumoral cell lines have shown the existence of new gastrin and glycine-extended gastrin receptors, other than the CCK_2, whose activation has a trophic effect, although they have not been completely characterized.[27,50–54]

In contrast to CCK_1, the signal-transduction cascade for CCK_2 receptors has been rather poorly characterized, in large part because of the difficulty of working with isolated neurons or isolated gastric mucosal cells expressing these receptors. Central CCK_2 receptors have not been proved to be linked to a well characterized second-messenger system in the brain, including the phosphoinositide system. However, in transfected cells (Cos, Chinese hamster ovary), it has been shown that like the CCK_1, the CCK_2 receptors couples to a pertussis toxin-insensitive G protein, causing activation of PLC, and subsequent formation of IP_3 and DAG, leading to the release of intracellular Ca^{2+} and the activation of PKC[23,27] (Table I).

CCK_1 and CCK_2 receptors share 48% amino acid identity,[27,34,45] having the main amino acid sequence differences in the intra- and extracellular loops and in the outer third of the transmembrane

domains adjacent to the extracellular space.[29,56–58] In spite of the high level of homology in the amino acid sequence for each CCK receptor subtype among species (72–80%), minor species-specific differences in receptor structure and distribution do occur that can result in significant pharmacological and physiological differences. In fact, mutagenesis studies in CCK receptors have shown that single amino acid substitutions may change ligand affinity[59,60] and, even, the agonist/antagonist functionality,[61] which in turn explain species-related differences. Therefore, it is important to consider the appropriate species for the intended experimental goals, and to be careful before extrapolating data from one animal species to another. Recently, several single nucleotide polymorphisms have been found in the gene structure of human cholecystokinin receptors, mainly in the CCK_2 subtype, which alter drug affinity and/or efficacy,[62] and it has been postulated that these polymorphisms may influence the susceptibility to CCK-related diseases, such as schizophrenia,[63] Parkinson's disease,[64] and obesity.[65] On the other hand, in both CCK_1 and CCK_2 receptors, some ligands have shown functional heterogeneity. Thus, CCK dose-response studies using pancreatic acini typically reveal a biphasic dose-response relationship: stimulation at low CCK concentrations and inhibition at supramaximal concentrations, as it is the case of the CCK_1 receptor mediated amilase release, protein synthesis, and adenosinetriphosphatase activity.[27] Initially, this biphasic activity was explained due to the existence of two different binding sites for CCK_1 receptors. Later, as the cloning studies on CCK_1 and CCK_2 receptors have failed to identified additional members of the CCK receptor family, their functional heterogeneity has been explained on the basis of the existence of different interconverting conformational states, with preferential or differential G protein coupling, and, therefore, distinct biological signal transduction and target cell function.[18,27] Studies with radiolabeled ligands, mainly by comparing results obtained from binding of agonists and antagonist, have shown that CCK_1 receptors exist in three different affinity states: the agonist [^{125}I]CCK-8 identified the high- and the low-affinity states, while the antagonist devazepide bound to the low-affinity state and to the very-low-affinity state, which represent 80% of the receptors.[18,66] Recently, it has been shown that, under physiological conditions, CCK acts on high- and low-affinity CCK_1 receptors present on distinct vagal afferent fibers.[67] CCK_2 receptors have also been shown to exist in three different affinity states.[18] Competition radioligand binding studies with diverse CCK_2 receptor antagonists have provided evidence for the existence of two binding sites, or binding states, for this receptor subtype in gastric glands and cortex of some animal species.[68–70] Furthermore, the distinct behavioral responses elicited by the CCK_2 selective agonists BC 197 (anxiogenic) and CB 264 (non-anxiogenic and increases memory and attention) have been also related with the existence of two different binding states of these receptors in the brain.[71,72]

3. CCK RECEPTOR ANTAGONISTS

The variety of physiological effects of CCK and its possible role in some pathological disorders have stimulated research in this area and, over the past decade, a number of potent and selective CCK_1 and CCK_2 receptor agonists and antagonists have been reported, which have highly contributed, as useful pharmacological tools, to the characterization of CCK receptor subtypes and for gaining insight into the functional significance of CCK in the periphery and in the CNS. The high therapeutic potentiality of some of these CCK receptor ligands have led them to clinical studies, and a few of them are considered very promising drug candidates. Thus, CCK_1 agonists have been studied as satiety agents in the treatment of obesity, while CCK_1 antagonists have been studied for the treatment of pancreatic and functional bowel disorders, gastroesophageal reflux, and pancreatic cancer. On the other hand, CCK_2 antagonists have been studied for the control of anxiety and gastric acid secretion, and for the treatment of drug tolerance. However, the involvement of CCK_2 receptor activation in gastric acid secretion and in the anxiogenic effects of CCK has discouraged the clinical studies of agonists for these receptor subtype. Several reviews covering diverse aspects of CCK receptor agonists and

antagonists have been published over the last years.[73–83] This article reviews the main advances in the development of CCK receptor antagonists, focusing mainly on those that have shown a greater pharmacological potential and those that could have a more promising therapeutic prospect.

Initially, most of the first CCK receptor antagonists were peptides or pseudopeptides derived from the structural modification of the amino acid sequence of CCK-7 and CCK-4. The *N*-Boc derivative of the C-terminal tripeptide, Boc-Met-Asp-Phe-NH_2, which inhibited the CCK-8-stimulated amylase release from guinea pig pancreatic acini with an IC_{50} of 0.25 mM,[84] was the first of these peptidic antagonists. Deletion of the C-terminal Phe^{33} residue from Boc-CCK-4[85] and Boc-CCK-7[86,87] derivatives produced CCK_2 and CCK_1 antagonists with binding affinities in the 10^{-6} M range. Replacement of the Met^{31} residue in these tri- and hexapeptide derivatives by Orn(Z) led to the CCK_1 receptor antagonists Boc-Trp^{30}-$Orn(Z)^{31}$-Asp^{32}-NH_2 and Boc-$Tyr^{27}(SO_3H)$-Nle^{28}-Gly^{29}-Trp^{30}-$Orn(Z)^{31}$-Asp^{32}-NH_2, which showed binding potencies in the 10^{-7} M range.[88] It is interesting to note that, as the replacement of the Met residues of CCK-4 and CCK-8 derivatives by Nle or Leu has no influence on their biological activity. Therefore, most of the synthetic CCK derivatives include this replacement to avoid the Met instability. The combined replacement of Phe^{33} by 2-phenylethyl ester[89] or amide,[90] and Trp^{30} by D-Trp in Boc-CCK-7 produced the most potent peptidic CCK_1 receptor antagonists with binding affinities at these receptors in the 10^{-8} range. On the other hand, the replacement of the Met^{31} and Phe^{33} residues of Boc-CCK-4 by the unnatural and hydrophobic amino acids phenylglycine (Phg) and dimethylamide-1-naphtylalanine [1-Nal-$N(CH_3)_2$], to increase metabolic stability and brain penetration, led to a CCK_2 antagonist with a binding affinity at CCK_2 receptors of 3.9×10^{-8} M.[91] Finally, within the pseudopeptide derivatives, replacement of the peptide bonds Nle^{31}-Asp^{32} in Boc-[Nle^{31}]-CCK-4 and Trp^{30}-Nle^{31} in Z-[Nle^{31}]-CCK-4 by the peptide bond surrogates $\psi[CH_2NH]$[92] and Ψ[CH(CN)NH],[93] led to CCK_2 antagonists, which displayed binding affinities in the range of 10^{-7} and 10^{-8} M, respectively. Similarly, the replacement of the Nle^{29}-Gly^{29} peptide bond in Boc-[$Nle^{28,31}$]CCK-7 by the peptide bond surrogates $\Psi[COCH_2]$ or Ψ[HNCO] gave the most potent peptidic CCK_2 antagonists, which displayed binding affinities in the subnanomolar range.[94] However, despite the very good potency and selectivity of some of these peptidic antagonists, their poor oral availability, low metabolic stability, difficulty to cross the blood–brain barrier, and, in some cases, their mixed antagonist/agonist character have hampered their therapeutic development. To avoid these problems, the search of CCK receptor ligands, both antagonists and agonists, has evolved towards the search of peptidomimetics or non-peptide ligands. The discovery in 1985 of the natural non-peptide compound asperlicin (**1**)[95] as a moderate, competitive, and selective antagonist of CCK_1 receptors ($IC_{50} = 10^{-6}$ M, pancreas binding)[96] represented a key breakthrough in this search. This finding opened the door to the search of peptidomimetics through random screening, not only in the CCK field, but in general in most peptide receptors. As it will be discussed later, the structure manipulation of asperlicin has led to the discovery of benzodiazepine and the quinazolidinone derivatives (Fig. 2) as two families of potent and selective CCK receptor antagonists. Over the past decade, antagonists with high structural diversity have emerged, which will be commented below grouped in structure families. In most of these groups, there are selective antagonists for CCK_1 and CCK_2 receptors, which will be discussed separately according to their selectivity.

A. Amino Acid Derivatives

1. CCK_1 Receptor Antagonists

Benzoyl-DL-glutamic acid dipropylamide, named proglumide (Table II, compound **3**), reported in 1967 by researchers at Rotta Laboratories as a weak gastrin antagonist,[97] could be considered as the first discovered CCK receptor antagonist. This compound, along with *p*-chlorobenzoyl-L-tryptophan (benzotript, **2**), was tested for its ability to antagonize the effects of CCK in 1981.[98,99] Both

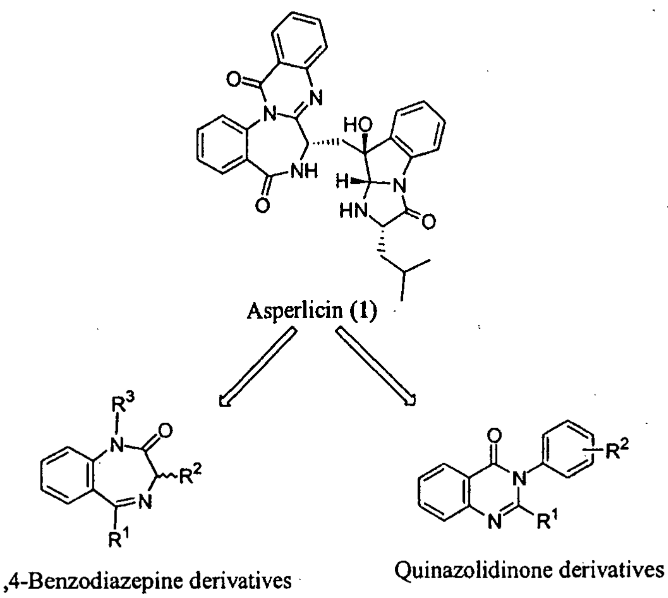
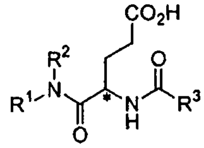


Figure 2. General structures of 1,4-benzodiazepine and quinazolidinone derivatives, potent and selective CCK receptor antagonist, derived from manipulation of the asperlicin structure.

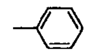
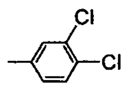
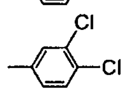
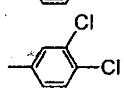
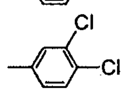
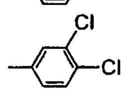
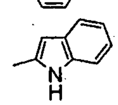
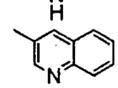
compounds were found to be weak competitive non selective antagonists of comparable potency in the inhibition of the [^{125}I]CCK-8 binding, the gastrin-stimulated gastric acid secretion, and CCK-stimulated amylase release from pancreatic acini. Proglumide has been marketed by Rotta Laboratories in Europe for the treatment of ulcers. Additional derivatives of tryptophan,[100] as well as simple analogues of most of the other coded amino acids,[101] have been investigated as potential CCK antagonists. However, it has been the group of the glutamic acid derivatives which, mainly by manipulation of the aromatic *N*-acyl group and the *N*-alkyl-carboxamide at the α-carboxy group, has provided the most potent and selective antagonists for both CCK_1 and CCK_2 receptors. To illustrate the rank order of potency, some of these compounds are summarized in Tables II and III with their binding affinity data. It must be noted that is not possible to do a precise quantitative comparison with data reported for different compounds, as they were issued from different research teams, sometimes using different animal species, tests, or experimental conditions. Therefore, these comparisons must be taken with precaution. On the benzoyl group of proglumide both steric and electronic effects, as well as regiochemistry, were explored with a variety of substituents.[102] The 3,4-dichloro substitution was which gave the most potent compounds. The alkyl amide groups were also found to play an important role. Thus, enlargement of the propyl groups of proglumide to *n*-pentyl, along with the 3,4-dichloro substitution at the benzoyl group, led to a higher than 10^4 increase in the CCK_1 binding affinity of lorglumide (**4**, CR 1409) a moderate and very selective CCK_1 antagonist, which displayed activity after oral administration and low toxicity.[103] As shown in Table II, the resolved D-enantiomer of this glutamic acid derivative is more potent at CCK_1 receptors than the corresponding L-enantiomer (compounds **5** and **6**). Loxiglumide (**7**, CR 1505), analogue of lorglumide in which an oxygen replaces one methylene, has shown very similar antagonistic properties to those of lorglumide.[104,105] Both compounds are moderately potent, competitive and selective CCK_1 receptor antagonists *in vitro* and *in vivo*, and are devoid of agonist activity.

In spite of the moderate potency of loxiglumide, its good pharmacokinetic properties and oral bioavailability have facilitated its use in pharmacological and clinical studies,[106] having been one of the CCK_1 antagonists more widely studied. Studies in animals have shown that this antagonist protects against experimental pancreatitis,[107] and these results were the basis for

Table II. Most Significant Selective CCK_1 Receptor Antagonists Derived From Amino Acids



3-10

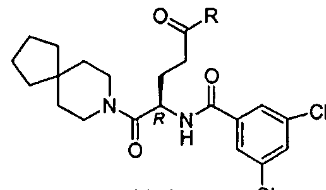
Compound	Config. (*)	R[1]	R[2]	R[3]	IC_{50} (μM) CCK₁	IC_{50} (μM) CCK₂	Selectivity CCK_2/CCK_1
Benzotript[a] (2)					82	40	0.49
Proglumide[a] (3)	DL	*n*-Pr	*n*-Pr		6,100	11,000	1.8
Lorglumide[a] (4) (CR 1409)	DL	*n*-Pentyl	*n*-Pentyl		0.13	300	2,307
D-Lorglumide[a] (5)	D	*n*-Pentyl	*n*-Pentyl		0.07	NR[b]	
L-Lorglumide[a] (6)	L	*n*-Pentyl	*n*-Pentyl		5.1	NR[b]	
Loxiglumide[c] (7) (CR 1505)	DL	$CH_3O(CH_2)_3$	*n*-Pentyl		0.33	9.1	27
Dexloxiglumide[c] (8) (CR 2017)	D	$CH_3O(CH_2)_3$	*n*-Pentyl		0.12	22	170
A-64718[d] (9)	D	*n*-Pentyl	*n*-Pentyl		0.02	1.30	68
A-65186[d] (10)	D	*n*-Pentyl	*n*-Pentyl		0.005	3.50	686

[a]Reference 103. Binding affinities in rat pancreatic acini (CCK_1) and mouse brain cortex (CCK_2), using the radioligand [^{125}I]CCK-8.
[b]NR = non reported.
[c]Reference 104.
[d]Reference 115. Binding affinities in guinea pig pancreas and brain, using the radioligand [^{125}I]CCK-8.

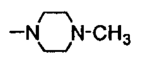
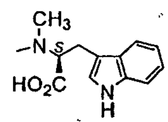
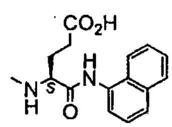
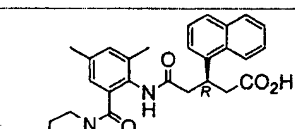
its clinical evaluation for the treatment of acute pancreatitis.[108] In healthy subjects loxiglumide inhibits the slow, but not the rapid phase of postprandial gall bladder contraction and accelerates gastric emptying.[109,110] It does not affect gastric motility or sensitivity during duodenal saline infusion, but partially restores gastric tonic activity during lipid infusion, reduces the occurrence of meal-like fullness and nausea, and increases the pressure at which sensations are reported.[111] Loxiglumide also inhibits the transient lower oesophageal sphincter relaxations and attenuates the fall in lower oesophageal sphincter (LES) pressure following a meal.[112] The injectable formulation of loxiglumide, for the treatment of acute pancreatitis, has been submitted for regulatory approval in Japan, and its oral formulation is undergoing Phase III trials for chronic pancreatitis.

Dexloxiglumide (**8**, CR 2017), retains all pharmacological properties of the racemic compound loxiglumide, but is more potent than this or its L-enantiomer. As loxiglumide, dexloxiglumide

Table III. Most Significant Selective CCK_2 Receptor Antagonists Derived From Amino Acids



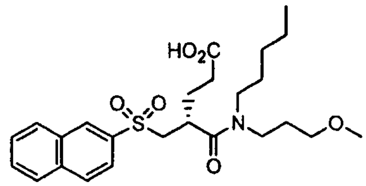
13-16

Compound	R	IC_{50} (nM) CCK$_1$	IC_{50} (nM) CCK$_2$	Selectivity CCK$_1$/CCK$_2$
Spiroglumide[a] (13) (CR 2194)	OH	13,500	1,400	9.6
CR 2345[b] (14)		6,600	700	9.4
CR 2767[a] (15)		3,400	57	60
CR 2622[a] (16)		7,380	20	369
 **17** Itriglumide[c] (CR 2945)		20,700	2.3	9,000

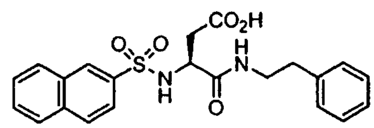
[a]Data reported in reference 125. Receptor binding affinities determined in rat pancreatic acini, using the radioligand [^{125}I]CCK-8 (CCK_1), and in guinea pig cortex, using the radioligand [^{3}H]-*N*-Me-*N*-Leu-CCK-8 (CCK_2).
[b]Data reported in reference 78. Receptor binding affinities determined as for **13**.
[c]Data reported in reference 127. Receptor binding affinities determined in rat pancreatic acini, using the radioligand [^{125}I]CCK-8 (CCK_1), and in rat cortex, using the radioligand [^{3}H]pBC264 (CCK_2).

has a good pharmacokinetic profile, and it has shown good safety and tolerability.[113] Results from both preclinical and clinical studies with this CCK_1 antagonist indicate that it is an effective inhibitor of gall bladder contraction, improves lower oesophageal sphincter function, and accelerates gastric emptying and colonic transit. Dexloxiglumide also significantly decreases symptoms in irritable bowel symdrome (IBS) and functional dyspepsia patients. Therefore, has potential as an effective treatment for constipation-predominant IBS, functional dyspepsia, constipation, LES function, gastric emptying disorders and biliary colics. Phase III studies with dexloxiglumide are in progress in USA, and Forest Laboratories has entered into an agreement with Rotta for its development and marketing. In June 2001, Merrill Lynch predicted an USA filing date for this compound in 2003.[114]

More potent CCK_1 antagonists have been discovered combining features of lorglumide and benzodiazepine structures,[115–117] such as A-64718 (**9**) and A-65186 (**10**), which showed nanomolar



11 (KSG-504)



12 (2-NAP)

Figure 3.

affinities at CCK_1 receptors, although data of pharmacological or clinical studies have not been reported. Additionally, the analogue of loxiglumide KSG-504[118] (Fig. 3, **11**), and the aspartic acid derivative 2-NAP[119,120] (**12**), both incorporating a 2-naphthalenesulphonyl group, have been described as competitive and selective CCK_1 antagonists, with binding affinities in the 10^{-7} M range, and they have been studied in Phase I clinical trials.

2. CCK_2 Receptor Antagonists

The structure modification of lorglumide also produced selective CCK_2 receptor antagonists.[121] Thus, spiroglumide (Table III, compound **13**) showed competitive and specific antagonism of the pentagastrin-stimulated gastric acid secretion in several animal species and models.[122] In humans, this CCK_2 antagonist dose-dependently antagonized gastrin-stimulated gastric acid and fluid responses with a competitive-like profile.[123] In a subsequent Phase I randomized, double-blind, placebo-controlled trial in healthy male volunteers, spiroglumide significantly decreased basal acid output in response to food ingestion as well as postprandial intragastric acidity.[124] However, despite its excellent oral bioavailability, the low affinity and selectivity at CCK_2 receptors (micromolar range) precluded further development of spiroglumide as a potential therapeutic tool for peptic ulcer diseases.[78]

The chemical manipulation of the structure of spiroglumide has led to more potent and selective CCK_2 antagonists.[125] Among these, the *N*-methylpiperazinyl derivative CR 2345 (**14**) was synthesized to investigate whether the acidic character of glutamic acid derivatives was essential for CCK_2 antagonism. The basic substitution in the carboxylic acid with the methylpiperazinyl group fully retains antagonistic activity. Moreover, CR 2345 also inhibited histamine- and carbachol-induced acid secretion.[126] Interestingly, this compound, as well as its *N*-propyl analogue (CR 2456), was shown to inhibit the growth *in vitro* of several human strains of *Helicobacter pylori*, isolated from patients with histological lesions of gastritis, now recognized as the aetiological factor of peptic ulcers, although the MICs of these spiroglumide derivatives were high (1-16 μg/ml) in comparison to those of the most effective antibiotics (e.g., the MIC_{50} range for clarithromycin is 0.03–0.3 μg/ml).[78] More potent and selective spiroglumide derivatives were obtained when the amino acids *N*-methyl-L-tryptophan (**15**, CR 2767) or L-glutamic acid *N*-(1-naphtyl)-amide (**16**, CR 2622) were coupled to the side chain carboxylic acid of spiroglumide.[125] Compound **16** given intravenously reduced dose-dependently the pentagastrin-stimulated gastric acid secretion in rat stomach. However, the relatively high molecular weight of this compound limits its oral absorption.[78] Further structure manipulation of CR 2622 has led to the anthranilic acid derivative itriglumide (**17**, CR 2945). This lower molecular weight analogue has improved *in vivo* oral bioavailability, and showed nanomolar affinity and excellent CCK_2 selectivity ($CCK_1/CCK_2 = 9{,}000$).[127] In vivo, itriglumide blocked pentagastrin-induced gastric acid secretion in anaesthetized rats with a 50% inhibitory dose of 0.3 mg/kg given intravenously, and 4.0 mg/kg given intraduodenum. In this type of administration, it was more potent than both ranitidine and omeprazole. The gastrin antagonism was reversible and competitive, with a pA_2 value of 7.33, and was gastrin-specific, as it was unable to antagonized the gastric acid secretion

stimulated by histamine or carbachol.[128] This compound also showed to be effective in prevention of gastric damage in several models.[78] Furthermore, itriglumide showed significant dose-dependent anxiolytic-like effects in four rodent tests of anxiety, comparable to those of the anxiolytic diazepam, but without signs of sedation and ataxia. Additionally, a 7-day repeated treatment with this compound at 10 mg/kg/day s.c. did not induced tolerance or withdrawal anxiety in rats.[128] Itriglumide also displayed antiproliferative effects in mice GI tumors.[129] In healthy volunteers, this CCK_2 antagonist was well tolerated, and now is in Phase I clinical studies as anxiolytic and antiulcer.

B. 1,4-Benzodiazepine Derivatives

1. CCK_1 Receptor Antagonists

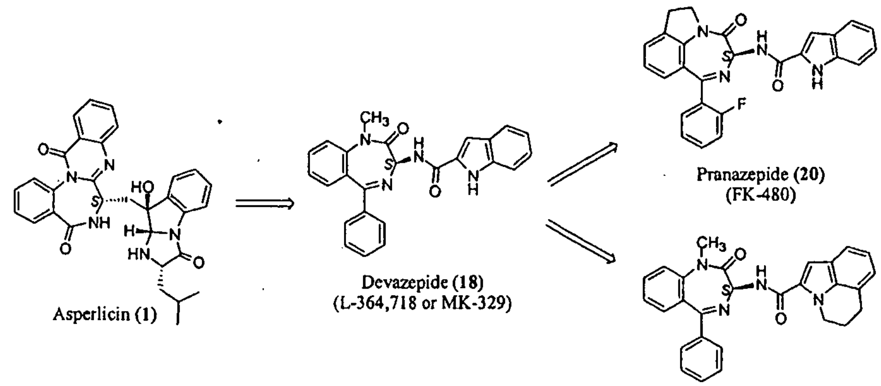
As it has been mentioned above, the chemical manipulation of asperlicin (**1**) structure, retaining the 1,4-benzodiazepine skeleton, has given very potent and selective antagonists for both CCK receptor subtypes CCK_1 and CCK_2. The first discoveries in this family of antagonists were made by Merck chemists, reasoning that combining the elements of diazepam with D-tryptophan might mimic asperlicin in its CCK receptor affinity. This idea proved to be very successful, obtaining the first non-peptide selective CCK_1 antagonists, which displayed similar affinity to that of asperlicin and oral activity.[130,131] Efforts to optimize the CCK_1 activity of these first benzodiazepine derivatives yielded the highly potent and selective antagonist devazepide (Table IV, compound **18**, also known as L-364,718 or MK-329).[132,133] This antagonist displays subnanomolar affinity at CCK_1 receptors, comparable to that of the native ligand CCK-8, and high selectivity versus the CCK_2. Devazepide has been shown to be highly potent by several routes of administration, including oral, in a variety of functional assays such as gastric emptying and gall bladder contraction in a number of different species, and no agonistic activity has been observed.[73] It has also been demonstrated that devazepide crosses the blood–brain barrier efficiently.[134,135] Due to its high potency, selectivity and bioavailability, devazepide has been the reference CCK_1 receptor antagonist more widely used as pharmacological tool for the study of the physiological effects of CCK and its receptors. In Phase I clinical trials, in healthy human volunteers, devazepide inhibited CCK-induced gall bladder contraction,[136,137] and stimulated gastric motility and gastric emptying after ingestion of meals, although this stimulation depends on the meal lipid content.[138] Although no data have been reported on Phase II clinical trials, Merck discontinued the development of devazepide in this phase in 2001, due to gallstone toxicity,[76,139] and it has been reported that this compound induces hyperplasia in the rat liver and bile ducts.[140] In spite of this, ML Laboratories and Panos Therapeutics have recently initiated a joint full Phase II clinical study of devazepide for the treatment of pain, in patients suffering from opioid-resistant neuropathic pain.

All the chemical modifications upon the devazepide structure have been detrimental both for the binding potency and for the selectivity at CCK_1 receptors. The inversion of the absolute configuration at the C-3 of the 1,4-benzodiazepine skeleton led to a two order of magnitude decrease in the CCK_1 potency for the enantiomer (*R*)-devazepide (Table IV, **19**). As it will be shown below, the decrease in CCK_1 selectivity with this inversion of configuration at C-3 is general in the 1,4-benzodiazepine-derived antagonists, and in most of them that configuration inversion produced a reversal of selectivity, leading to CCK_2 selective antagonists. Among the devazepide analogues developed as CCK_1 antagonists, pranazepide (FK-480, **20**)[141,142] and tarazepide (**21**)[143,144] have reached Phase II clinical trials, although no data are available in the peer-reviewed literature about the results of these compounds in human clinical studies.

2. CCK_2 Receptor Antagonists

Researchers at Merck also discovered the first highly potent and selective non-peptide CCK_2 receptor antagonist L-365,260 (Table V, compound **22**) in the process of asperlicin structure manipulation,

Table IV. Most Significant 1,4-Benzodiazepine-Derived Selective CCK_1 Receptor Antagonists



Asperlicin (1)

Devazepide (18) (L-364,718 or MK-329)

Pranazepide (20) (FK-480)

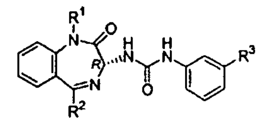
Tarazepide (21)

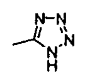
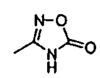
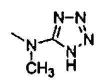
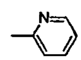
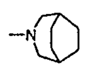
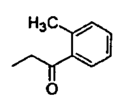
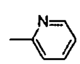
Compound	IC_{50} (nM) CCK_1[a]	CCK_2[b]	Selectivity CCK_2/CCK_1	Reference
Asperlicin (1)	1,400	$>10^5$	>71	130
Devazepide (18) (L-364,718 or MK-329)	0.08	270	3,375	133
(*R*)-Devazepide (19)	8.3	3,700	446	133
Pranazepide (20) (FK-480)	0.67	310	463	141
Tarazepide (21)	NR[c]	NR[c]		143

[a]Binding affinities in rat pancreas, using the radioligand [^{125}I]CCK-33 except for **20** that [^{125}I]CCK-8 was used.
[b]Binding affinities in guinea pig brain, using the radioligand [^{125}I]CCK-33 except for 20 that [^{125}I]CCK-8 was used.
[c]Data not reported.

through the combination of replacing the indol-2-yl-amide of devazepide by an aryl urea moiety at the 1,4-benzodiazepine C-3 position and the (*R*) stereochemistry at that position.[145] That compound, which displayed nanomolar affinity at CCK_2 receptors and 140-fold selectivity versus the CCK_1, also represented a significant landmark in the pharmacological studies of CCK and its receptors. Upon oral administration, it potently antagonized gastrin-stimulated acid secretion in several animal species with good duration of action.[146] However, in Phase I clinical trials in healthy male volunteers, L-365,260 produced only a modest inhibition of gastrin-stimulated gastric acid secretion, and this effect was of short duration.[147] In spite of the predominant role of CCK_2 receptors in the anxiogenic effects of CCK, L-365,260 has not clearly showed anxiolytic activity in animal models.[10] In Phase II clinical studies, this antagonist achieved a significant reduction in the frequency and intensity of CCK-4[148] and lactate-induced[149] panic attacks in patients with panic disorders, and has shown to reverse the autonomic and anxiogenic effects of pentagastrin in healthy volunteers.[150] However, in another study, it was ineffective in limiting panic attacks in patients.[151] These discouraging clinical results were attributed to its limited oral bioavailability, wich could be explain by its low aqueous solubility.[152,153] Based on the modest results of L-365,260 in the inhibition of gastric acid secretion, Merck researchers envisaged only a marginal role in the antiulcer therapy for this CCK_2 antagonist, and searched for other analogues with greater CNS penetration and oral bioavailability with the aim of successfully controlling anxiety and panic disorders. This goal was pursued through the incorporation of bulkier substituents at the N-1 position and water-solubilizing groups into the structure of L-365,260. Thus,

Table V. Most Significant 1,4-Benzodiazepine-Derived Selective CCK_2 Receptor Antagonists



Compound	R^1	R^2	R^3	IC_{50} (nM) CCK_1[a]	CCK_2[b]	Selectivity CCK_1/CCK_2	Reference
L-365,260 (**22**)	CH_3	Phenyl	CH_3	280	2.0	140	145
23[c]	$CH_2CON(Et)_2$	Phenyl	OCH_3	120	0.22	545	154
L-708,474 (**24**)	CH_3	Cyclohexyl	CH_3	1,797	0.28	6,418	155
L-368,730 (**25**)	CH_3	Phenyl		577	1.0	577	156
L-369,466 (**26**)	CH_3	Phenyl		983	0.27	3,640	156
L-736,380 (**27**)	CH_3	Cyclohexyl		400	0.05	8,000	157
28[c]	CH_3		CH_3	65	66	1	154
L-740,093 (**29**)	CH_3		CH_3	1604	0.10	16,040	161
YM022 (**30**)		Phenyl	CH_3	150[d]	0.11[e]	1,364	163
YF476 (**31**)	$CH_2COC(CH_3)_3$		$NHCH_3$	502[d]	0.11[e]	5,020	168

[a]Inhibition of the binding of [^{125}I]CCK-8 to rat pancreas tissues.
[b]Inhibition of the binding of [^{125}I]CCK-8 to guinea pig cerebral cortex.
[c](*3RS*)-Stereochemistry.
[d]Inhibition of the binding of [^{3}H]L-364,718 to rat pancreas membranes.
[e]Inhibition of the binding of [^{125}I]CCK-8 to rat cerebral cortex.

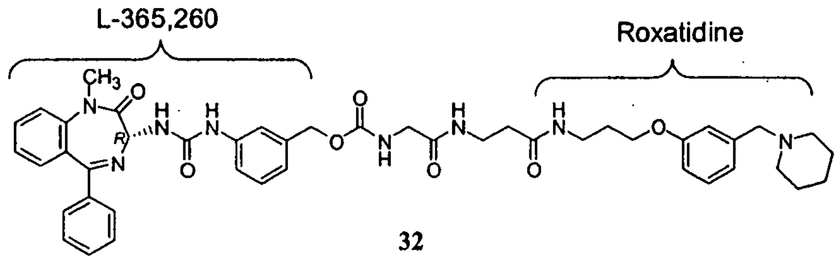
more potent analogues were obtained either by the introduction of a diethyl acetamide group at N-1 as in **23**[154] (Table V), or by saturation of the 5-phenyl substituent to the cyclohexyl in L-708,474[155] (**24**). However, the water solubility of these compounds was also very low. In the second-generation benzodiazepines this issue was resolved, whilst maintaining the increased receptor affinity, firstly by replacing the 3-methyl substituent on the aryl urea moiety by acidic solubilizing groups such as the tetrazol or 1,2,4-oxadiazol-2-one rings.[156] Prominent compounds emerging from this series include the tetrazole derivatives L-368,730 (**25**) and L-368,935, and the oxadiazolone analogue L-369,466 (**26**). However, despite the excellent potency and increased solubility, these compounds did not exhibit satisfactory bioavailability. Therefore, further modifications were performed on the tetrazole moiety of L-368,730 in order to influence bioavailability by modulating the pK_A of the acidic moiety by means of structural manipulations around the tetrazole group.[157] From this study, the amino-tetrazole group was chosen as acidic moiety, because its pK_A (6.0) is substantially higher than that of the tetrazole itself. Compounds resulting from this strategy, such as L-736,380 (**27**) and its analogue L-738,425, in which a 2-tetrazolyl-isoindolyl moiety replaces the 3-(*N*-methyl-*N*-tetrazolyl)amino-phenyl of **27**, are among the most potent and, in the case of L-738,425 [CCK_2 IC_{50} = 0.11 nM, CCK_1/CCK_2 = 37,000], most selective CCK_2 antagonists so far reported. L-736,380, given by the

intraperitoneal route, dose-dependently inhibited the gastric acid secretion in anaesthetized rats, with an ID_{50} of 0.064 mg/kg. However, these acidic compounds are significantly less brain penetrant than the prototype L-365,260 (**22**).[157]

Only with the introduction of cationic water solubilizing groups, particularly within the C-5 substituent, the oral bioavailability was improved. Such strategy was initially prompted by the 4-fold increase in plasma concentration after oral dosing in rats, with respect to L-365,260, achieved in the case of the 2-pyridyl substituted derivative **28**.[154] This change was accompanied by a reduction in receptor affinity and selectivity, and although this was restored by the introduction of bulkier substituents into the N-1 position, there was a concomitant reduction in aqueous solubility from this change, which was reflected in decreased plasma concentration with respect to L-365,260 upon oral administration. The optimization of this strategy has provided several improved compounds,[158–160] standing out among them L-740,093 (**29**), where the introduction of the bulky basic 2-azabicyclo[3.2.2]non-2-yl moiety into C-5 increased both receptor affinity and aqueous solubility.[161] According to its *in vitro* affinity, log D (4.7), aqueous solubility (0.15 mg/ml at pH = 5.0), and pK_A (7.1), L-740,093 was 100-fold more potent than L-365,260 in inhibition of pentagastrin-stimulated acid secretion upon i.p. administration.[161]

Although the second generation of 1,4-benzodiazepine-based CCK_2 receptor antagonists have superseded L-365,260 in terms of their *in vivo* properties in animal models, corresponding data in humans have so far not been reported. The recognition by Merck that L-365,260 and related 1,4-benzodiazepine-based CCK_2 receptor antagonists blocked the slowly activating component (I_{Ks}) of delayed rectifier potassium currents in guinea pig myocytes,[162] and the association of this effect with cardiac arrhythmia, may have restricted subsequent clinical studies.

Yamanouchi in collaboration with Ferring developed the finding that CCK_2 receptor affinity of 1,4-benzodiazepine-based antagonists increased on introducing bulky substituents at the N-1 position. The optimal compound of this series, YM022 (**30**), which contains a 2-methyl-benzoylmethyl group at this position, showed subnanomolar affinity at rat brain CCK_2 receptors, more than 2 orders of magnitude higher than that for rat pancreatic CCK-A receptor.[163] *In vivo*, this compound inhibits gastrin-stimulated acid secretion in anaesthetized rats by i.v. administration (ED_{50} = 7.8 nM/kg).[164] Although YM022, as the other 1,4-benzodiazepines which contain bulky substituents at N-1, suffers from low aqueous solubility and requires formulation as a solid dispersion to achieve adequate oral bioavailability,[165] by this route was as effective as the histamine H_2-antagonist famotidine and 8-fold more potent than the prototypical proton pump inhibitor omeprazole in models of gastric and duodenal ulcer in rats. YM022 had no effect on histamine or bethanechol-stimulated gastric acid secretion.[166] Moreover, YM022, given orally, was able to practically inhibit gastric damage induced by restraint stress, and inhibited the hypersecretion observed following cessation of omeprazole treatment.[167] These results supported the assertion that this compound may have a role as an alternative anti-ulcer therapy devoid of the risk in relapse, and promoted YM022 to Phase I clinical studies. Greater aqueous solubility and oral bioavailability was achieved by the introduction of basic groups, by replacing either the 5-phenyl group by a 2-pyridyl substituent, or the 3-methyl group of the aryl urea moiety by a methylamino group as in YF476[168] (**31**, also known as YM-220). This compound has shown similar binding potency at CCK_2 receptors to YM022, but 5-fold higher selectivity with respect to CCK_1. By i.v. administration, YF476 displayed similar behavior to YM022 and was 15- and 4-fold more potent than famotidine in the inhibition of gastrin-stimulated acid secretion in anaesthetized rats and Heidenheid pouch dogs, respectively.[169] In this last animal model, YF476 was almost as effective by oral as by i.v. administration.[168] In rats, YF476 completely reversed the hypergastrinemia and cell proliferation caused by omeprazole and gastrin in ulcerated gastric mucosa.[170] Moreover, this antagonist showed a prolonged duration of action upon oral[168] and subcutaneous[171] administration. On account of the good pharmacological profile of YF476 in *in vivo* animal models, Yamanouchi and Ferring chose to evaluate this compound for the treatment of gastro-oesophageal reflux disease (GORD), and as YM022 is in Phase I clinical studies.



32

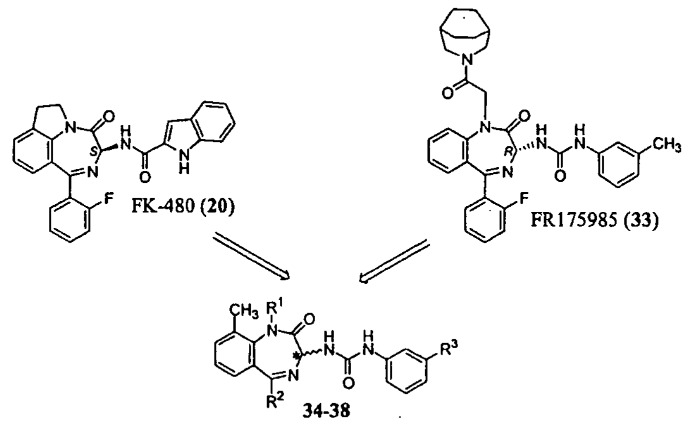
Figure 4.

In an attempt to alleviate the relapse problem, frequently encountered in the chemotherapy of peptic ulcers with histamine H_2 receptor antagonists, researchers at Shionigi designed and synthesized hybrid compounds of the H_2 receptor antagonists famotidine or roxatidine and the CCK_2 antagonist L-365,260, using different spacers to joint both types of antagonists.[172,173] Applying this strategy, they obtained dual CCK_2/H_2 antagonists such as compound **32** (Fig. 4), which showed a pA_2 value of 6.8 for the histamine H_2 receptor and an IC_{50} value of 19 nM for the CCK_2 receptor. However, although these compounds showed good gastric acid antisecretory activities by i.v. administration, in the oral route these activities were much lower, indicating low oral bioavability.[174]

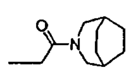
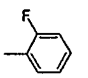
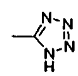
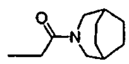
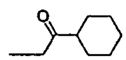
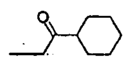
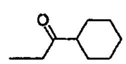
3. Dual CCK_1/CCK_2 Receptor Antagonists

Researchers at Fujisawa postulated that dual antagonists of CCK_1 and CCK_2 receptors might be more efficacious for the treatment of pancreatitis than selective CCK_1 antagonists, based on the following reasons. CCK_1 receptor antagonists inhibit pancreatic exocrine secretion on the one hand, whilst they also stimulate gastric acid secretion, through the inhibition of the CCK_1 receptor mediated somatostatin release from D cells of the gastric mucosa, which in its turn stimulates pancreatic exocrine secretion. Additionally, it is known that lowering of pH in the duodenum by gastric acid is one of the important factors in accelerating pancreatic exocrine secretion, which is considered to be an exacerbating factor of pancreatitis. Accordingly, gastric acid secretion inhibitors such as histamine H_2 blockers and proton pump inhibitors are often prescribed for the treatment of pancreatitis. This hypothesis was supported by the fact that the joint administration of the CCK_1 antagonist FK-480 and the CCK_2 antagonist YM022 inhibited more profoundly the casein-stimulated pancreatic exocrine secretion than both compounds in separated treatment.[175] To study this hypothesis, several 1,4-benzodiazepine-based dual CCK_1/CCK_2 receptor antagonists were designed combining structural elements of FK-480 (**20**) and FR175985 (Table VI, compound **33**), potent and selective antagonists of CCK_1 and CCK_2 receptors, respectively. In this design, it was considered that the incorporation of additional groups into the 9 position of the 1,4-benzodiazepine skeleton of FR175985 (**33**) would introduce steric repulsion between substituents at 1 and 9 positions, forcing to the 1,4-benzodiazepine system to adopt a similar structure to that in FK-480, leading to a possible dual antagonism. Among the different alkyl groups incorporated into position 9, the methyl group was chosen as it gave the best binding results at CCK_1 and CCK_2 receptors.[176] The first compounds of this series bound to both receptor subtypes with nanomolar potency, but had poor water solubility. To improve this issue, maintaining binding potencies, similar strategies to those previously commented for other 1,4-benzodiazepine derivatives were applied, such as introduction of acidic groups into the aryl urea moiety, as in the tetrazole derivative FR193108 (**34**).[175] This compound showed potent binding affinity at both receptors, but it was found to be only poorly absorbed upon oral administration in rats. In order to improve bioavailability, this lead compound was optimized by synthesizing analogues with a lower molecular weight, reducing the size of the substituents at positions 1 and 5. The

Table VI. Most Significant 1,4-Benzodiazepine-Derived Dual CCK_1/CCK_2 Receptor Antagonists



FK-480 (20) FR175985 (33) **34-38**

Compound	Config. (*)	R^1	R^2	R^3	IC_{50} (nM) CCK_1[a]	CCK_2[b]	Selectivity CCK_1/CCK_2
FK-480 (**20**)	*S*	--	--	--	0.67	310	0.002
FR175985 (**33**)	*R*	--	--	--	62	0.087	712
FR193108 (**34**)	*R*				9.2	0.38	24
FR196979 (**35**)	*RS*		CH_3	CH_3	2.2	0.68	3.2
FR202893 (**36**)	*RS*		CH_2-CH_3	CH_3	0.9	1.6	0.56
FR208418 (**37**)	*S*		CH_2-CH_3	CH_3	8.2	7.8	1.05
FR208419 (**38**)	*R*		CH_2-CH_3	CH_3	0.3	1.0	0.3

[a]Inhibition of [^{125}I]CCC-8 binding to rat pancreatic membranes.
[b]Inhibition of [^{125}I]CCC-8 binding to guinea pig cerebral cortical membranes.

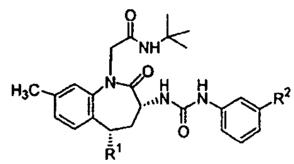
5-substituent can be exchange by a methyl or ethyl group without loss in the binding affinities at both receptors. However, the size of the 1-substituent cannot be significantly reduced without decreasing the binding potency at CCK_2 receptors. The comparison of the binding data for the racemic compound **36** and both resolved enantiomers **37** and **38** shows the importance of the (*R*)-configuration at C-3 for the binding to both receptor subtypes. The activity of FR208419 (**38**) after oral administration, estimated from the ID_{50} value (0.23 mg/kg) obtained in preliminary evaluation in gastric emptying effects, was considered to be high enough for further biological evaluations with view to clinical development.[177]

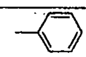
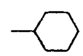
C. Benzazepine-Based CCK_2 Antagonists

By analogy with the 1,4-benzodiazepines, 1-benzazepin-2-ones have also been used as templates in the design of CCK_2 receptor antagonists. Initial examples lacked the potency and selectivity afforded by their 1,4-benzodiazepine-based analogues,[178] but after a parallel structural optimization some very

potent antagonists were developed.[179] Thus, CP212,454 (**39**) (Table VII) exhibited higher CCK_2 receptor affinity than L-365,260 and was 367-fold selective over CCK_1 receptors. In guinea pigs, this compound potently inhibited pentagastrin-induced gastric acid secretion with a lower ED_{50} (0.8 mg/kg s.c.) than L-365,260 ($ED_{50} = 1.5$ mg/kg s.c.).[179] However, its low water solubility suggests a probable poor oral bioavailability. Modification of the structure of **39**, by replacing the 5-phenyl group by a cyclohexyl and inserting ionizable groups such as a carboxylic acid led to the analogue CP310,713 (**40**). This compound showed improved water solubility and *in vivo* efficacy ($ED_{50} = 0.03$ mg/kg s.c. in the pentagastrin-induced gastric acid secretion model).[180] However, its low efficacy in preclinical studies led to stop the development of CP310,713 (**40**).[83]

Table VII. Significant 1-Benzazepine-2-one-Based CCK_2 Receptor Antagonists



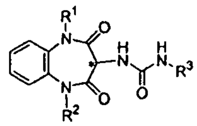
Compound	R¹	R²	IC₅₀ (nM) CCK₁ᵃ	IC₅₀ (nM) CCK₂ᵇ	Selectivity CCK₁/CCK₂	Reference
CP212,454 (**39**)		Cl	176	0.48	367	179
CP310,713 (**40**)		CO_2H	1,400	0.10	14,000	180

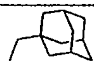
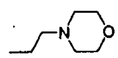
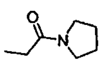
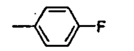
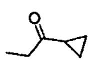
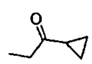
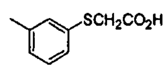
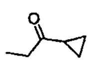
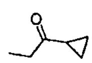
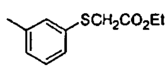
ᵃInhibition of [^{125}I]CCC-8 binding to guinea pig pancreatic membranes.
ᵇInhibition of [^{125}I]CCC-8 binding to guinea pig cortex.

D. 1,5-Benzodiazepine-Based CCK_2 Antagonists

The introduction of functional assays, along with radioligand binding assays, in high throughput screenings by Glaxo's researchers allowed them the discovery of a series of 1,5-benzodiazepine derivatives as the first non-peptide CCK_1 receptor agonists.[181] In these random screenings, some of the compounds showed CCK_2 antagonist activity, which was optimized introducing substituents into the 1,5-benzodiazepine skeleton similar to those found successful in the Merck 1,4-benzodiazepine antagonists. Lead compounds were obtaining by positioning an aryl urea moiety at C-3 and locating branched or bulky groups at N-1 and N-5 positions. Structure-activity relationship (SAR) studies, as in the 1,4-benzodiazepine series, showed a similar influence of the absolute configuration at C-3 on the binding potency, being the (*R*)-enantiomers more potent at CCK_2 receptors.[182] Among these compounds GV150013X (Table VIII, compound **41**) was the first selected for pharmacological development. In the guinea pig myenterium plexus, where both CCK_2 and CCK_1 receptors are found GV150013X antagonized the CCK-4-induced contractions with a pK_B of 8.9, while for the inhibition of CCK_1 agonist-induced contractions the pK_B was 5.9. In the isolated gastric mucosa, this compound also showed antagonistic activity in the pentagastrin-induced gastric acid secretion, although was less potent with a pK_B of 7.4.[182] *In vivo*, GV150013X has shown dose-related anxiolytic effects in several animal models.[183] In all the anxiety models used, this antagonist displayed similar efficacy to the dipeptoid CCK_2 antagonist PD134,308 and to the standard benzodiazepine diazepam, without tolerance or rebound anxiogenesis upon withdrawal after chronic treatment (7 days at 0.3 μg/kg, p.o.) observed with diazepam. In general pharmacological studies, GV150013X did not showed effect up to 3 mg/kg, p.o. in the rota-rod test, in the passive avoidance, and on pentobarbitone sleeping time.[182]

Table VIII. More Significant 1,5-Benzodiazepine-Based CCK_2 Receptor Antagonists



Compound	Config. (*)	R[1]	R[2]	R[3]	Affinity CCK_1	Affinity CCK_2	Selectivity CCK_1/CCK_2	Ref.
GV150013X (41)	*R*		Phenyl	Phenyl	pK_i[a] 6.15	pK_i[b] 8.64	309	182
GV191869X (42)	*R*			Phenyl	pK_i[a] 5.70	pK_i[b] 9.40	4,988	81
GV199114X (43)	*S*		Cyclohexyl		pK_i[a] 7.10	pK_i[b] 8.60	40	185
44	--				IC_{50}[c] 500	IC_{50}[d] 2.0	250	186
45	--				IC_{50}[c] 460	IC_{50}[d] 6.0	77	186

[a]pK_i values of inhibition of the binding of [^{3}H]CCK-8 to rat pancreatic membranes.
[b]pK_i values of inhibition of the binding of [^{3}H]CCK-8 to guinea pig cerebral cortex membranes.
[c]IC_{50} nM values of the binding of [propionyl-^{3}H]CCK-8 to mouse pancreas.
[d]IC_{50} nM values of the binding of [propionyl-^{3}H]CCK-8 to mouse cortical membranes.

Additionally, GV150013X improved sleep in aged rats, without detecting tolerance after chronic treatment, while development of tolerance towards benzodiazepines was monitored following chronic treatment with triazolam.[184] Based on these results, GV150013X has progressed to Phase II clinical trials for anxiety and sleep disorders, although no data are currently available.

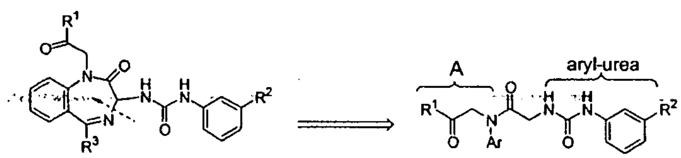
In order to improve physicochemical properties of GV150013X, the phenyl group at the N-5 position was replaced by a morpholinoethyl substituent to give GV191869X (**42**). This analogue showed improved solubility and was a more potent and selective CCK_2 antagonist.[81] GV191869X (**42**) also exhibited anxiolytic activity in both the mouse light/dark box and in the marmoset 'human threat' test models, maintaining a significant effect in the dose range of 0.01–10 μg/kg.[81] Similarly, GV199114X (**43**) also showed improved aqueous solubility and oral bioavailability. This antagonist was equipotent by i.v. (60% at 0.3 mg/kg) and oral administration in the inhibition of pentagastrin-induced gastric acid secretion in rats.[185] Although based on the *in vivo* potency and plasma pharmacokinetics this compound could be a suitable candidate to investigate the actions of peripheral CCK_2 receptors, this may be hampered by the low receptor selectivity margin (40-fold, based on radioligand binding affinities).

By choosing identical substituents at both N-1 and N-5 positions of the 1,5-benzodiazepine template, Shionogi avoided the need for enantiomer resolution or stereoselective synthesis. Optimization of this substituent identified cyclopropylcarbonyl-methyl as the preferred one. When this substituent was combined with the introduction of acid groups into the aryl urea moiety, such as the thioacetic acid of compound **44**, the CCK_2 receptor affinity was comparable to that of L-365,260.[186] However, *in vivo*, the optimum compound of this series was the ethyl ester derivative **45** which showed potent inhibition of pentagastrin-induced gastric acid secretion in anaesthetized rats, with an ED_{50} value of 0.06 mg/kg upon intraduodenal administration, being almost twice more potent that L-365,260 and YM022 in this assay.[186]

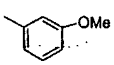
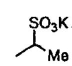
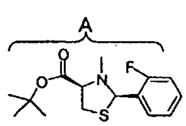
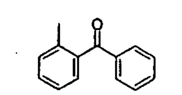
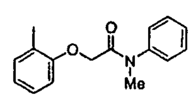
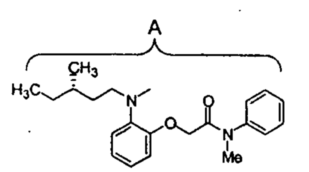
E. Ureidoacetamide CCK_2 Antagonists

The ureidoacetamide-based CCK_2 receptor antagonists may be considered acyclic analogues of the 1-carbonylmethyl-1,4-benzodiazepine-derived antagonists, resulting from the opening of the C_3-N_4 bond. Most of these ureidoacetamide analogues exhibited similar biological properties to those of their 1,4-benzodiazepine parent compounds. The first of these compounds were described by Rhône-Poulenc,[187] such as RP 69758 (Table IX, compound **46**), which displayed comparable binding potency in guinea pig cortex to L-365,260, but based on ex vivo binding studies did not significantly penetrate the CNS.[188] The replacement of the acetic acid moiety in R^2 by ethyl sulphonate and the introduction of a methoxy group into the phenyl group led to a 10-fold increase in the CCK_2 receptor affinity and selectivity for RP 73870 (**47**).[189] This increase in the *in vitro* affinity was also observed in the *in vivo* assays. This compound was 10-fold more potent that the dipeptoid CI-988 in the inhibition of gastrin-stimulated gastric acid secretion in the in situ perfused rat stomach

Table IX. Significant Ureidoacetamido-Based CCK_2 Receptor Antagonists



46-51

Compound	R^1	Ar	R^2	Affinity CCK_1	Affinity CCK_2	Selectivity CCK_1/CCK_2	Reference
RP 69758 (**46**)	NHPh	Ph	CH_2CO_2H	K_i^a 1,254	K_i^b 9.0	139	188
RP 73870 (**47**)	NMePh			K_i^a 1,634	K_i^b 0.48	3,404	189
RPR1011367 (**48**)			CH_2CO_2H	--	K_i^b 3	--	83
S-0509 (**49**)	OtBu		CH_2CO_2Na	IC_{50}^c 3,400	IC_{50}^d 42	81	190
DA-3934 (**50**)	NMePh		CH_2CO_2H	IC_{50}^e 877	IC_{50}^f 0.4	2,193	192
D51-9927 (**51**)			CH_2CO_2H	IC_{50}^e 172	IC_{50}^f 0.06	2,867	193

[a] K_i (nM) inhibition of the binding of [propionyl-^{3}H]CCK-8 to guinea pig pancreas.
[b] K_i (nM) inhibition of the binding of [propionyl-^{3}H]CCK-8 to guinea pig cortex.
[c] IC_{50} (nM) inhibition of the binding of [propionyl-^{3}H]CCK-8 to mouse pancreas.
[d] IC_{50} (nM) inhibition of the binding of [propionyl-^{3}H]CCK-8 to mouse cortical membranes.
[e] IC_{50} (nM) inhibition of the binding of [^{125}I]CCK-8 to human CCK_1 receptors.
[f] IC_{50} (nM) inhibition of the binding of [^{125}I]gastrin to human gastrin receptors.

($ID_{50} = 0.05$ mg/kg i.v., 3 mg/kg p.o.). Unlike RP 69758, compound **47** did not inhibited basal acid secretion at concentrations required to inhibit the gastrin-induced secretion. Moreover, in models of gastric ulceration in rats, RP 73870 specifically inhibited acid-dependent mechanisms, being as effective as the proton pump inhibitor omeprazole and ineffective in models of ethanol-, restraint stress- or insulin-induced ulceration. Rhône-Poulenc also designed restricted analogues of their ureidoacetamides such as RPR1011367 (**48**) to investigate CCK_2-mediated behavioural effects in animal models. This antagonist inhibited the CCK-8-stimulated firing of rat hippocampal neurons with a 4- and 10-fold higher potency than CI-988 and L-365,260, respectively, and this higher potency was also observed *in vivo*, where this compound displayed anxiolytic-like effects in the elevated X-maze test.[83]

Shionogi also designed ureidoacetamides in which a benzophenone moiety was introduced to keep a greater similarity with the 1,4-benzodiazepine structure.[190] Among the compounds of this series, S-0509 (**49**) afforded the optimum balance of receptor affinity and selectivity and *in vivo* potency. On anaesthetized pylorus-ligated rats this antagonist was about 30- and 200-fold more potent than L-365,260 by i.v. ($ED_{50} = 0.001$ mg/kg) and intraduodenal (0.003 mg/kg) administration, respectively. Unlike L-365,260 and YM022, S-0509 did not enhanced morphine analgesia on the tail flick test. This result prompted Shionogi researchers to conclude that S-0509 has poor blood–brain permeability and, because of that, could be a good tool to distinguish between peripheral and central effects of CCK_2 antagonism. S-0509 is currently found at Phase I clinical trials for gastric secretion disorders.

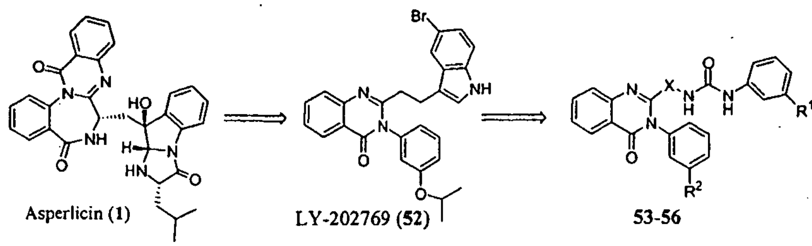
Researchers at Daiichi have also reported on ureidoacetamide-based CCK_2 antagonists that include a phenoxyacetic acid moiety in their structure.[191–193] For example, DA-3934[192] (**50**) and D51-9927[193] (**51**), which potently inhibited the [^{125}I]gastrin binding to CHO cells transfected with human CCK_2 receptors. In lumen-perfused anaesthetized rats D51-9927 inhibited pentagastrin-stimulated acid secretion by i.v. ($ED_{50} = 0.004$ mg/kg) and intraduodenal routes ($ED_{50} = 0.5$ mg/kg). Chronic administration (28 days) of this antagonist to rats (3, 30 mg/kg/day, p.o.), together with omeprazole (60 mg/kg/day, p.o.), inhibited the hypersecretory response to gastrin-G17, otherwise observed on cessation of omeprazole treatment.[83]

F. Quinazolinone-Based CCK_2 Antagonists

The strategy of manipulating the asperlicin structure, by appropriate bond disconnections, retaining the quinazolinone and indole templates, led Lilly's researchers to the discovery of another family of potent and selective CCK_2 antagonists.[194] The lack of chiral centers in this series of compounds significantly facilitated the structure optimization, from which LY-202769 (Table X, compound **52**) was selected as the best compound, although the reported pharmacological results of this compound are limited to its effect on midbrain dopamine activity.[195] The reported SAR study showed the importance of the isopropyloxyl substituent at the *meta* position of the 3-phenyl group as well as the size and flexibility of the carbon chain linker between the quinazolinone and indole templates.[194,196]

Parke-Davis also pursued this design approach, maintaining the quinazolinone skeleton, but replacing the 3-alkyl-indole moiety by an aryl urea. The first compounds of this series, such as **53** and **54**, showed only moderate binding potency and selectivity at CCK_2 receptors,[197] which were significantly improved by replacing the methylene bridge by a NH, as in compounds **55** and **56**.[198] As in LY-202769, the presence of the *meta*-isopropyloxy group, or other of similar size as the dimethylamino of **56**, is important both for the potency and selectivity. The presence of electron-withdrawing substituents in position 3 of the phenylurea group also significantly enhanced the CCK_2 potency. Both compounds **55** and **56** showed anxiolytic-like effects in the rat X-maze test after oral administration, although their lower effective dose (1.0 mg/kg) was 10-fold higher than that of the reference compound LY-202769 (**52**) (0.1 mg). Both compounds **55** and **56** showed poor aqueous solubility and, as consequence, the estimated bioavailability of **55** was $< 5\%$, while that of **56** was 22% after oral administration.[198]

Table X. Significant Quinazolinone-Based CCK_2 Receptor Antagonists



Asperlicin (1) LY-202769 (52) 53-56

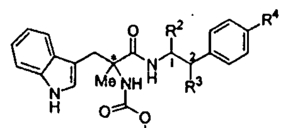
Compound	X	R[1]	R[2]	IC_{50} (nM) CCK_1[a]	CCK_2[b]	Selectivity CCK_1/CCK_2	Reference
LY-202769 (52)	--	--	--	$>10^4$	9.3	>1,075	194
53	CH_2	CH_3	O*i*Pr	1,637	879	1.9	197
54	CH_2	CO_2Et	O*i*Pr	1,465	126	11.6	197
55	NH	CO_2tBu	O*i*Pr	2,960	1.9	1557	198
56	NH	CN	$N(Me)_2$	7,100	14	507	198

[a]IC_{50} for inhibition of [^{3}H]-L-364,718 (**52**) or [^{125}I]CCK-8 binding to rat pancreas.
[b]IC_{50} for inhibition of [^{125}I]CCK-8 binding to mouse brain membranes.

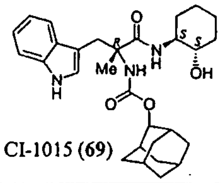
G. Dipeptoids

Researchers at Parke-Davis used the C-terminal tetrapeptide sequence of CCK (CCK-4) as a starting point for the rational design of CCK_2 receptor ligands. This design was based on the finding that the Trp and Phe residues were the minimum and necessary sequence to impart micromolar affinity at CCK_2 receptors[199] (Table XI). They adopted the strategy of sequentially optimizing both the N- and C-terminal residues of the Boc-Trp-Phe-NH_2 dipeptide. The resulting dipeptide analogues were designed as 'dipeptoids'.[200] As shown in Table XI, the N-terminus SAR studies revealed that the replacement of Trp by α-methyl-tryptophan, together with bulky cycloalkyl carbamate groups at this residue were preferred. Among these bulky groups, the 2-adamantyloxycarbonyl was the optimum.[200] These studies also showed that modifications at the tryptophan indole ring were not well tolerated.[201] Keeping constant in the structure the *N*-(2-adamanyloxycarbonyl)-α-methyltryptophan residue, the C-terminus optimization was focused on the incorporation of carboxylic acid-containing groups at positions 1 and 2 of the 2-phenylethylamine moiety.[202] CI-988 (also named PD-134,308, **58**) emerged from this SAR study as the most potent and selective CCK_2 antagonist of this series. This compound and its analogue CAM1189 (**59**) blocked the pentagastrin-stimulated gastric acid secretion by iv infusion of 0.5 and 0.07 μmol/kg, respectively.[202] Compound **59** was equipotent by i.v. and s.c. administration ($ED_{50} = 0.07$ μmol/kg), being more potent than the H_2 receptor antagonist ranitidine ($ED_{50} = 0.19$ μmol/kg). The replacement of the CI-988 carboxylic acid by some bioisosteric groups, such as the sulphonic acid of compound **60** did not significantly affected the CCK_2 binding affinity, although these replacements reduced the CCK_1/CCK_2 selectivity of the resulting compounds.[203] Based on its higher CCK_2 selectivity versus CCK_1 receptors, CI-988 was chosen for studies on its behavioral effects on the CNS. In these studies, CI-988 exhibited potent anxiolytic effects in several animal models of anxiety, including the mouse black/white box test, the rat plus maze and social interaction tests, and the marmoset human threat test.[204] These effects were comparable in magnitude to those produced by diazepam, but, unlike diazepam, CI-988 did not produced sedation, and there was no evidence of development of tolerance or any sign of withdrawal anxiogenesis after abrupt termination of the treatment. However, these anxiolytic effects have not been confirmed in Phase II clinical trials in patients with generalized anxiety and panic disorders.[205–208] Neither has CI-988

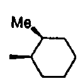
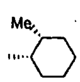
Table XI. Significant Dipeptoid CCK Receptor Antagonists



57-68



CI-1015 (69)

Compound	Config. *	1	2	R^1	R^2	R^3	R^4	IC_{50} (nM) CCK_1[a]	CCK_2[b]	Selectiv[c]	Ref.
CCK-8								0.12	0.27	0.44	
CCK-4								5,330	2.6	2,050	
BocTrp-PheNH$_2$								--	73,000[d]	--	199
57	*RS*	--	--	1-Ad[e]	H	H	H	--	5,000[d]	--	200
CI-988 (58) (PD-134,308)	*R*	--	*R*	2-Ad[f]	H	HNCO(CH$_2$)$_2$CO$_2$H	H	4,300	1.7	2,529	202
CAM1189 (59) (PD-136,450)	*R*	--	*R*	2-Ad	H	HNCOCH=CHCO$_2$H	H	709	0.7	1,100	202
60	*R*	--	*R*	2-Ad	H	HNCO(CH$_2$)$_2$SO$_3$Na	H	1,010	1.3	780	203
PD-135,666 (61)	*R*	*S*	--	2-Ad	CH$_2$CO$_2$H	H	H	25.1	0.15	170	219
CAM 1481 (62) (PD-140,548)	*S*	*R*	--	2-Ad	CH$_2$CO$_2$H	H	H	2.82	260	0.01	219
PD-140,547 (63)	*S*	*S*	--	2-Ad	CH$_2$CO$_2$H	H	H	539	13.2	41	219
PD-140,723 (64)	*R*	*R*	--	2-Ad	CH$_2$CO$_2$H	H	H	186	9.3	20	219
PD-149,164 (65)	*R*	*S*	--	2-Ad	CH$_2$CO$_2$H	H	F	75	0.08	938	220
66	*R*	*S*	--	2-Ad	CH$_2$CO$_2$H	H	NO$_2$	225	0.19	1,184	220
67	*S*	*R*	--		CH$_2$CO$_2$H	H	H	7.9	1,160	0.007	219
68	*R*	*S*	--		CH$_2$CO$_2$H	H	H	3.9	4.2	1	219
CI-1015 (69)	*R*	*S*	*S*	2-Ad	--	--	--	2,900	3.0	967	215

[a]IC_{50} for inhibition of [^{125}I]CCK-8 binding to rat pancreas membranes.
[b]IC_{50} for inhibition of [^{125}I]CCK-8 binding to mouse cortex membranes.
[c]Selectivity, CCK_1/CCK_2.
[d]K_i value for the inhibition of [^{3}H]-Boc-β-alanyl-CCK-4 binding to mouse cortex membranes.
[e]1-Ad = 1-adamantyl.
[f]2-Ad = 2-adamantyl.

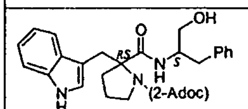
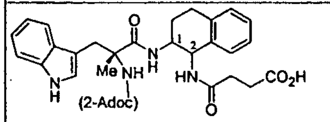
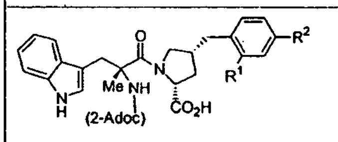
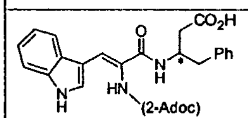
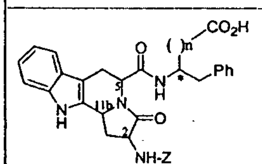
shown significant anxiolytic effects on lactate-[209] and CCK-4-induced[210] panic symptoms in healthy volunteers. These poor results, along with the reported CCK_2 partial agonist activity on histidine decarboxylase in rat stomach enterochromaffin-like cells[211] and on stomach histamine release and acid secretion,[212] as well as the full CCK_1 agonist activity on the amylase release in the rat pancreas,[213] have hampered the further clinical development of CI-988. In diabetic rats, CI-988 enhanced the analgesia induced by morphine,[214] and induced antinociceptive effects on mechanical hyperalgesia.[215]

The lack of anxiolytic effects of CI-988 in humans has been attributed to its low bioavailability,[210,216] in part due to its high molecular weight. Therefore, to improve the pharmacokinetic profile, the structure of CI-988 was modified with the aim of reducing the molecular weight and improving the aqueous solubility and absorption, maintaining the binding potency and selectivity at CCK_2 receptors. As the *N*-(2-adamantyloxycarbonyl)-α-methyl-D-tryptophan moiety is critical for affinity, modifications were focused on the C-terminus.[216] These modifications led to the identification of the analogue CI-1015 (Table XI, **69**),[216] which showed similar CCK_2 binding affinity that CI-988, although with lower selectivity versus CCK_1 receptors. This compound exhibited CCK_2 antagonist profile in the rat ventromedial hypothalamus assay with a K_e of 34 nM. It also showed an anxiolytic like profile orally in the standard anxiety (X-maze) paradigm with a minimum effective dose of 0.1 μg/kg. Although CI-1015 was less water soluble than CI-988, the oral bioavailability in rats was improved nearly 10 times when dosed as a solution in hydroxypropyl-β-cyclodextrin. The blood–brain permeability was also enhanced relative to CI-988. On the basis of the overall improved pharmacokinetic profile,[117] CI-1015 was chosen as a development candidate, although results on clinical studies have not been reported.

Additional SAR studies have demostrated the importance of the central amide bond between the N- and C-terminus of these dipeptoids for their CCK_2 binding potency and selectivity.[118] On the other hand, the diasteroisomeric dipeptoids substituted at position 1 of the phenyl-ethylamine moiety **61–64** (Table XI) have proved the stereochemical preference for each receptor subtype.[219] Thus, the stereoisomer **61** (PD-135,666) was a potent and selective CCK_2 antagonist in the electrophysiological test on the rat ventromedial nucleus of the hypothalamus, with a K_e value of 2.8 nM, and was also anxiolytic in the mouse light/dark box test with a minimum dose of 0.01 mg/kg, s.c. On the contrary, its enantiomer **62** (PD-140,548) was a selective and competitive CCK_1 antagonist, which inhibited the CCK-8-evoked amylase release from rat pancreatic acinar cells with a K_e value of 16 nM.[219] In the *trans*-2-methylcyclohexyl derivatives **67** and **68** the reversal of the stereochemistry transformed the CCK_2 antagonist **67** into the mixed CCK_1/CCK_2 antagonist **68**, which showed antagonist properties in both CCK_1 and CCK_2 models. Introduction of small electron withdrawing substituents, such as F or NO_2, into the *para* position of the phenyl group of compound **61** increased affinity and selectivity at CCK_2 receptors in the analogues **65** and **66**.[220] It is interesting to note that compound **65** (PD-149,164) was a potent antagonist at CCK_2 receptors and showed full CCK_1 agonist activity *in vivo* in the exocrine pancreas of rats and *in vitro* in rat pancreatic acini, while its enantiomer was a CCK_1 antagonist.[221]

With the aim of developing pharmacophore models of the dipeptoid-CCK receptor recognition or proving conformational hypothesis, conformationally constrained analogues have also been designed. Among these analogues, the use of a proline ring to constrain the tryptophan residue led to a significant decrease in the binding potency at CCK_2 receptors and reversal of the selectivity towards CCK_1 receptors in compound **70** (Table XII).[222] Perhaps the low affinities of this compound could have been improved after the resolution of the epimeric mixture at the proline stereogenic center. Restriction of the phenyl group rotation in CI-988, by incorporation of a tetrahydronaphtyl group into the phenyl-ethylamine moiety, led to a decrease of approximately 10-fold in the CCK_2 selectivity for the diastereoisomeric analogues **71** and **72**.[223] The proline ring has also been used to restrict the C-terminus in compounds **73–75**.[224] These compounds also displayed reduced CCK_2 affinity and selectivity, but it is worthy of note that, although the three compounds exhibited comparable CCK_2

Table XII. Conformationally Constrained Dipeptoid CCK Receptor Antagonists

Compound	N°	Configuration / Substituents	Affinity (nM) CCK_1	Affinity (nM) CCK_2	Selectivity CCK_1/CCK_2	Reference
 70	70		1,050[a]	2,080[b]	0.50	222
	71	Configuration: 1 *S*, 2 *R*	460[a]	2.31[b]	199	223
	72	Configuration: 1 *R*, 2 *R*	1,690[a]	6.16[b]	274	223
	73	R^1 = Cl, R^2 = Cl	749[c]	45.7[d]	16.4	224
	74	R^1 = F, R^2 = F	394[c]	17.6[d]	22.4	224
	75	R^1 = H, R^2 = NO_2	2,104[c]	26.3[d]	80	224
	76	* = *S*	18[a]	0.30[b]	60	225
	77	* = *R*	3.9[a]	60[b]	0.065	225
	78	Configuration: 2 *S*, 5 *S*, 11b *R*, * *S*; n = 0	4.7[e]	>10,000[f]	<0.0005	227
	79	Configuration: 2 *R*, 5 *R*, 11b *S*, * *S*; n = 0	1.7[e]	202[f]	0.008	227
	80	Configuration: 2 *S*, 5 *S*, 11b *R*, * *R*; n = 1	7.4[e]	2,700[f]	0.003	226

[a] IC_{50} for inhibition of the [^{125}I]CCK-8 binding to rat pancreas membranes.
[b] IC_{50} for inhibition of the [^{125}I]CCK-8 binding to mouse cortex membranes.
[c] K_i values for inhibition of the [propionyl-^{3}H]CCK-8 binding to guinea pig pancreas membranes.
[d] K_i values for inhibition of the [propionyl-^{3}H]CCK-8 binding to guinea pig cortex membranes.
[e] IC_{50} for inhibition of the [propionyl-^{3}H]CCK-8 binding to rat pancreas membranes.
[f] IC_{50} for inhibition of the [propionyl-^{3}H]CCK-8 binding to rat cortex membranes.

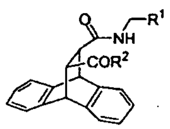
affinities on guinea pig cortex and on rat brain CCK_2 receptor expressed in CHO cells, they inhibited the CCK-8-induced inositol phosphate production in these cells with rather different IC_{50} values (37.4, 389, and 507 nM for **73–75**). The approximate 10-fold discrepancy observed in the antagonistic activity of compound **73** with respect to **74** and **75**, has been attributed to differences in the binding at two affinity states of CCK_2 receptors.[224] As shown in Table XII, the enantiomeric compounds **76** and **77**, where a α,β-didehydrotryptophan replaces the α-methyl-tryptophan, provided additional evidence of the stereoselectivity in the binding to both receptor subtypes.[225] The highly CCK_1 selective compounds **78–80** were designed based on the hypothesis that the folding of the peptide backbone of dipeptoids into a β-turn-like conformation could contribute to their bioactive conformation at CCK_1 receptors.[226,227] These compounds incorporate the 2-amino-3-oxohexahydroindolizino[8,7-*b*]indole-5-carboxylate scaffold, a probed β-turn mimetic, as replacement of the α-methyl-tryptophan. This design strategy has provided the most potent and selective CCK_1 antagonists in the dipeptoid series.

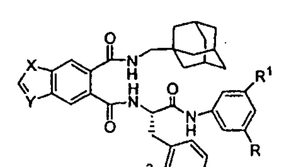
H. Dibenzobicyclo[2.2.2]octane and Bicycloheteroaromatic Scaffold-Based CCK_2 Antagonists

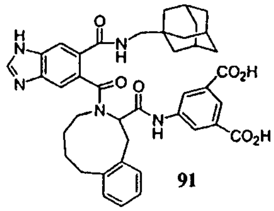
James Black Foundation' researchers have also designed a series of selective CCK_2 receptor antagonists based on the topography of the CCK-4 structure. They looked for rigid skeletons that

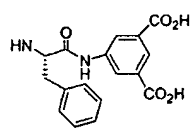
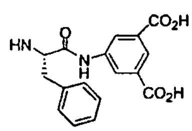
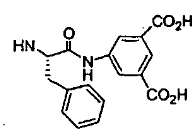
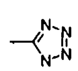
could replace the peptide backbone of this tetrapeptide while maintaining the stereoelectronic features obtained from molecular mechanic calculations and fluorescence studies on CCK-4. From this basis, they proposed that the two aromatic rings of the tryptophan and phenylalanine side chains of CCK-4 are interacting in a π-stacking arrangement with a separation of 5–7 Å, and designed the dibenzobicyclo[2.2.2]octane (BCO) scaffold as mimic of the peptide backbone.[228] One of the fused phenyl rings of this skeleton could mimic one of the aromatic side chains, and a second aromatic group would be appended as part of the R^1 moiety in compounds **81–85** (Table XIII). Some of the initial compounds of this series, exemplified by the proline derivatives **81** and **82**, exhibited submicromolar affinity for CCK_2 receptors, and selectivity > 60-fold over the CCK_1 receptors.[228] The first SAR

Table XIII. Dibenzobicyclo[2.2.2]octane and Bicycloheteroaromatic Scaffold-Based CCK_2 Receptor Antagonists


81-85


86-90


91

Compound	X	Y	R^1	R^2	pK_i CCK_1[a]	CCK_2[b]	Selectiv. CCK_1/CCK_2	Ref.
81	--	--	1-Ad[c]	D-Pro-Gly	4.83	6.67	69	228
82	--	--	1-Ad[c]	L-Pro-D-Ala	4.62	7.39	589	228
83	--	--	1-Ad[c]		5.68	8.80	1,318	229
84	--	--	Cyclohexyl		5.30	7.76	288	229
85	--	--	2-Naphtyl		5.79	8.57	603	229
JB93182 (**86**)	NH	CH_2	H	CO_2H	5.44	8.96	3,311	230
87	S	CH_2	H	CO_2H	5.65	8.91	1,820	230
88	NH	N	H	CO_2H	5.83	8.28	282	230
89	NH	CH_2	F	CO_2H	5.48	9.13	4,467	230
90	NH	CH_2	H		5.89	8.92	1,072	230
91	NH	N	--	CO_2H	4.74	8.30	3,631	234

[a] pK_i values for the inhibition of the binding of [^{125}I]CCK-8 to guinea pig pancreas.
[b] pK_i values for the inhibition of the binding of [^{125}I]CCK-8 to mouse cortical homogenates.
[c] Ad, adamantyl.

studies on this series showed that, among several bulky alicyclic and aromatic groups incorporated into R^1, the 1-adamantyl group was the optimum. The replacement of the proline residue by L-phenylalanine and the glycine or alanine residues by the 3,5-dicarboxyanilide group, to give compounds **83–85**, produced an increase of, at least, one order of magnitude in the binding affinity at CCK_2 receptors. At least one of the carboxylic groups of these compounds is crucial for high binding affinity, and altering the chain length of the phenylalanine residue is detrimental to the binding.[229] Interestingly, compounds **83–85** showed species-variation when evaluated *in vivo* for their ability to antagonize pentagastrin-stimulated gastric acid secretion in rats and dogs. For example, the adamantly derivative **83**, when administered intravenously, was 700-fold less active in chronic gastric fistula dogs hat in Ghosh and Schild anaesthetized rats.[230] This discrepancy prompted further modification to identify a replacement for the BCO framework. This research resulted in a new series of *ortho*-disubstituted bicyclic heteroaromatic analogues which maintained the affinity and selectivity demonstrated by the BCO derivatives, but gave a more consistent *in vivo* profile.[230] Thus, for example, the indole derivative JB93182 (Table XIII, compound **86**) was as potent as the BCO analogue **83** in the pentagastrin-stimulated gastric acid secretion model in anaesthetized rats, but exhibited similar potency in chronic gastric fistula dogs. The *in vivo* species-variable behavior exhibited by the BCO derivatives could be due to the interspecies variation in CCK receptors already commented in the introductory heading 2. JB93182 dose-dependently inhibited the gastrin-stimulated histidine decarboxylase activation in intact fasted rats with a ID_{50} value of 8 nmol/kg i.v., 4-fold lower than that shown by the benzodiazepine derivative YF476.[231] Similarly, JB93182 inhibited the gastrin-induced secretion of pancreastatin, a chromogranin A-derived peptide, from isolated rat enterochromaffin-like (ECL) cells with a IC_{50} value of 9.8 nM.[232] Both activities are related with the blockage of CCK_2 receptors in ECL cells.[233]

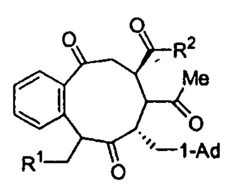
To study the conformational preference of the phenylalanine side chain, this residue was replaced in compound **88** by conformationally restricted phenylalanine analogues, which integrate the phenyl and amino groups into different size rings.[234] In general, this structure modification was detrimental for the binding at CCK_2 receptors, except for the analogue **91** which showed similar *in vitro* profile to that of its model **88**.

Based on the same design strategy that led to the BCO-derived antagonists, a new series of antagonists based on the 2,7-dioxo-2,3,4,5,6,7-hexahydro-1-*H*-benzo[*h*][1,4]-diazonine scaffold has recently been reported.[235] The initial compounds of this series, such as compounds **92** and **93** (Fig. 5), have shown moderate affinities at CCK_2 receptors, similar to that exhibited by the first members of the BCO family.

It is remarkable that a simple *N*-methylation at the indolic N–H in JB93182 (**86**) gave rise to an agonist activity of acid secretion stimulation in isolated lumen-perfused mouse stomach, without significantly affecting the binding affinity at CCK_2 receptors.[236] This easy switch from antagonist to agonist functionality suggests that both the agonist and the antagonist might share a common recognition site at the receptor.

I. 1,3-Dioxoperhydropyrido[1,2-c]pyrimidine-Based CCK_1 Antagonists

The CCK-4 structure was also the starting point for the search of CCK antagonists at the Medicinal Chemistry Institute of Madrid. In this case, researchers focused their attention on the design of



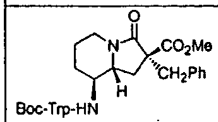
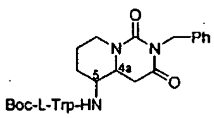
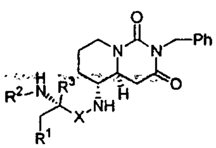
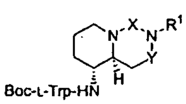
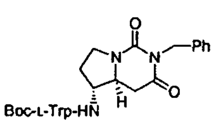
	R^1	R^2	CCK_2 (pK_i)
92	2-Cl-Ph	Gly	6.99
93	2-Cl-Ph	L-Ala	7.33

Figure 5.

conformationally restricted analogues, using bicyclic lactam skeletons as replacements for the central dipeptide [Met^{31}-Asp^{32}] of CCK-4. Some of the first compounds resulting from this approach, which included a 3-oxoindolizidine skeleton as a spacer between the Trp^{30} and Phe^{33} residues, represented by compound **94** (Table XIV), showed micromolar affinity at CCK_1 or CCK_2 receptors depending on the stereochemistry.[237] Based on these results, the structure of the initial compounds was manipulated by replacing the 3-oxoindolizidine skeleton by analogue rigid frameworks which could impart to the aromatic side chains a more appropriate spatial orientation at the receptor recognition site. Particularly, the use of the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine scaffold led to the discovery of a family of highly potent and selective CCK_1 receptor antagonists.[238] The prototype of this group of antagonists IQM-95,333 (**95**) showed nanomolar CCK_1 affinity, comparable to that shown by devazepide (**18**) in the same assay, but with a higher selectivity, as it was devoid of affinity at brain CCK_2 receptors at the highest concentration assayed (10^{-5} M). This compound inhibited the CCK-8-stimulated amylase release from rat pancreatic acini with similar potency (IC_{50} = 21.3 nM) to that of devazepide (IC_{50} = 25.4 nM).[239] As a CCK_1 antagonist, IQM-95,333 also inhibited the contractile response induced by CCK-8 in the guinea pig ileum with a comparable potency (pK_B = 8.4) to that of devazepide (pK_B = 8.5). Low doses (50–100 μg/kg, i.p.) of this antagonist, blocked the hypophagia and the hypolocomotion induced by systemic administration of CCK-8 in rats, two effects associated with the stimulation of peripheral CCK_1 receptors. Interestingly, IQM-95,333 exhibited an anxiolytic-like profile in the light/dark exploration test in mice over a wide dose range (10–5,000 μg/kg, i.p.), while the CCK_1 and CCK_2 antagonists devazepide and L-365,260, respectively, were effective only within a more limited dose range (2–100 μg/kg and 2–100 μg/kg i.p.). The three antagonists IQM-95,333, devazepide and L-365,260 also showed anxiolytic-like effects in the rat punished-drinking test (Vogel test), although within a narrow dose range.[239] Although the anxiolytic effects of devazepide have previously been attributed to the blockage of CCK_2 receptors at high doses (IC_{50} = 270 nM[133]),[240] this explanation can not be applied to IQM-95,333, as this compound is devoid of affinity at this receptor subtype. Therefore, these results support previous suggestions that CCK_1 receptors may also be involved in anxiogenesis.[241–243]

To define the pharmacophore of this perhydropyrido[1,2-*c*]pyrimidine-based family of CCK_1 antagonists a thorough SAR study on the three structural domains (tryptophan, central bicyclic skeleton, and substituent at N2-position) was carried out. This study showed the importance of the (4a*S*,5*R*)-stereochemistry at the 1,3-dioxoperhydropyrido[1,2-*c*]-pyrimidine template (compare compounds **95-98**, Table XIV) and the L-configuration at the tryptophan residue as essential requirements for CCK_1 binding affinity and subtype receptor selectivity.[238] The presence of the *tert*-butoxycarbonyl group (Boc) and the amide bond, or an appropriate H-bonding surrogate such as ψ[CH(CN)NH] (**105**), were also critical for the binding at CCK_1 receptors, while the replacement of the tryptophan residue by other aromatic amino acids, such as Phe (**99**) or α-Me-Trp (**100**) led to more than 10-fold decrease in the binding potency.[244] Interestingly, the replacement of the acid-labile Boc group by their bioisosters *tert*-butylaminocarbonyl (**103**) or 3,3-dimethylbutyryl groups conferred acid stability and a longer antagonism of the CCK-8-induced hypomotility in mice by oral administration. Moreover, compound **103** by intraperitoneal or oral administration showed protective effect on experimental acute pancreatitis induced by caerulein in rats.[244] Respecting the N2-substituent, the SAR study indicated the importance of its lipophilic character and an appropriate spatial orientation. Thus, the benzyl group at this position in the prototype **95** was replaced by cyclohexyl, phenyl, or naphtyl groups without affecting binding affinity and selectivity, while its replacement by methyl group led to almost the complete loss of the binding affinity.[245] It is interesting to note the existence of atropoisomerism in the 2-naphtyl derivatives, and that, among the two epimers at this position, the (2*S*)-compound **111** was 26-fold more active than its (2*R*)-epimer (IC_{50} = 15.4 nM). This difference between both epimers shows the importance of the aryl group orientation. In general, the insertion of substituents with different electronic or steric properties into

Table XIV. 1,3-Dioxoperhydropyrido[1,2-*c*]pyrimidine-Based CCK_1 Receptor Antagonists

Compound						IC_{50} (nM) CCK_1[a]	CCK_2[b]	Selectiv. CCK_2/CCK_1	Ref.
CCK-8						1.04	5.60	5.4	244
	94					2,350	>10,000	>4	237
	N°			Configuration 4a	5	K_i (nM)			
	IQM-95,333 (95)			*S*	*R*	0.62	>5,000	>8,000	238
	96			*R*	*S*	10.6	2,730	257	
	97			*R*	*R*	576	>5,000	>8	
	98			*S*	*S*	2,890	2,910	1	
	N°	X	R^1	R^2	R^3	IC_{50} (nM)			
	95	CO	In[c]	Boc	H	1.59	>10,000	6,300	
	99	CO	Ph	Boc	H	65.7	>10,000	152	
	100	CO	In[c]	Boc	Me	42.4	>10,000	236	
	101	CO	In[c]	H	H	>1,000	>10,000	---	244
	102[d]	CO	In[c]	2-Adc[e]	H	340	3,430	10	
	103	CO	In[c]	tBu-HNCO	H	0.91	>10,000	>11,000	
	104	CH_2	In[c]	Boc	H	>1,000	>10,000	---	
	105	[(*R*)CHCN]	In[c]	Boc	H	7.69	>10,000	>1,300	
	N°	X	Y	R^1		IC_{50} (nM)			
	106	CO	CO	Me		9,162	>10,000	>1	245
	107	CO	CO	Cyclohexyl		0.60	>10,000	>16,700	245
	108	CO	CO	Ph		1.18	>10,000	>8,500	245
	109	CO	CO	(*S*)-CH(CH_3)Ph		6.89	>10,000	>1,450	245
	110	CO	CO	2-(Me)Ph		0.97	>10,000	>10,300	245
	111	CO	CO	1-Naphtyl		0.59	>10,000	>17,000	245
	112	CS	CO	CH_2Ph		0.09	>10,000	$>10^5$	246
	113	CS	CS	CH_2Ph		1.34	>10,000	7,500	246
	114	CO	CS	CH_2Ph		2.83	>10,000	3,500	246
	115	CH_2	CO	CH_2Ph		>1,000	>10,000	---	246
	116	CO	CH_2	CH_2Ph		>1,000	>10,000	---	246
	117					>1,000	>10,000	---	246

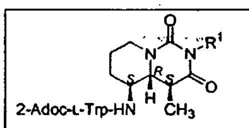
[a]IC_{50} or K_i values for the inhibition of the binding of [propionyl-^{3}H]CCK-8 to rat pancreas.
[b]IC_{50} or K_i values for the inhibition of the binding of [propionyl-^{3}H]CCK-8 to rat cerebral cortex membranes.
[c]In = indol-3-yl.
[d](4aR,5S)-stereochemistry.
[e]2-Adc = 2-adamantyloxycarbonyl.

the phenyl group of compound **108** led to (2–50)-fold reduction in the binding affinity at CCK_1 receptors, independently on the nature of the substituent.[245]

Modifications at the central 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine skeleton have indicated that, whereas the replacement of the 1- or/and 3-oxo groups of IQM-95,333 by the thioxo analogues (compounds **112-114**) is allowed, the reduction of these groups (**115** and **116**) or the contraction of the fused piperidine ring to the pyrrolidine analogue (**117**) led to the complete loss of the binding affinity.[246] These results gave further support for the crucial influence of the topography defined by the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine scaffold, with a (4a*S*,5*R*)-stereochemistry upon the binding to CCK_1 receptors. The 1-thioxo derivative **112**, with subnanomolar affinity (0.09 nM), even higher than that of the endogenous ligand CCK-8, and $> 10^5$-fold selectivity over the CCK_2 receptors, is the most selective and one of the most potent CCK_1 antagonists reported up to now.

The high CCK_1 selectivity of the 1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine-based CCK antagonists has recently been reversed towards the CCK_2 receptors by combination of configuration inversion at this bicyclic heterocyclic system, replacement of the Boc group by the 2-adamantyloxycarbonyl, and insertion of a methyl group into the (4*S*)-position, such as in compounds **118** and **119** of Table XV.[247]

Table XV. 1,3-Dioxoperhydropyrido[1,2-*c*]pyrimidine-Based CCK_2 Receptor Antagonists

			IC_{50} (nM)		Selectivity	
	N°	R^1	CCK_1[a]	CCK_2[b]	CCK_1/CCK_2	Ref.
	**118**	CH_2Ph	>10,000	181	>83	247
	119	4-[$N(CH_3)_2$]Ph	>10,000	121	>55	247

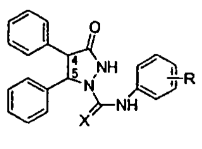
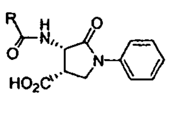
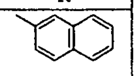
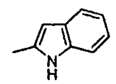
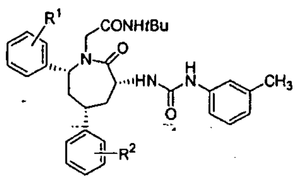
[a]IC_{50} for the inhibition of the binding of [propionyl-^{3}H]CCK-8 to rat pancreas.
[b]IC_{50} for the inhibition of the binding of [propionyl-^{3}H]CCK-8 to rat cerebral cortex membranes.

J. Pyrazolidinone and Related Heterocyclic-Derived CCK Antagonists

Efforts to optimize lead compounds through random screening used at the Lilly company resulted in the discovery of diphenylpyrazolidinone derivatives with nanomolar affinity at CCK_1 and CCK_2 receptors as compounds LY294920 (Table XVI, **121**, X = S) and LY288513 (**120**, X = O), respectively.[248] In the rat stomach, the CCK_2 antagonist LY288513 (**120**) did not inhibited the gastrin-induced activation of histidine decarboxylase.[249] However, this compound produced anxiolytic-like effects in mice and rats.[250–252] In the elevated plus-maze test, this antagonist showed an anxiolytic effect in mice of comparable potency to diazepam, used as a reference standard. However, unlike diazepam, LY288513 did not affect muscle tone, neuromuscular coordination, or sensorimotor reactivity. High doses of this compound were required to reduce spontaneous activity levels, decrease body temperature, or potentiate the CNS-depressant effects of hexobarbital. LY288513 had no analgesic activity in mouse writhing or tail-flick tests. Electrophysiological studies in anaesthetized rats showed that acute administration of LY288513 decreased the number of spontaneously active dopamine neurons in the substantia nigra and ventral tegmental area, but did not produce catalepsy. These results indicated that LY288513 could possess both anxiolytic and antipsychotic potential.[250] Moreover, LY288513 blocked the effects of nicotine[253] and diazepam[254] withdrawal in rats. However, the development of LY288513 was discontinued because of adverse effects in preclinical toxicological studies.[78]

Researchers at Searle employed 1,3,5-trisubstituted pyrrolidinones as scaffolds for appending groups which could mimic amino acid side chains of CCK-4.[255] This approach led to CCK_1 antagonists represented by SC-50,998 (**122**) and **123** (Table XVI). The carboxylic acid of these compounds is essential for binding affinity. SC-50,998 competitively inhibited the CCK-8-stimulated

Table XVI. Pyrazolidinone and Related Heterocyclic-Based CCK Antagonists

Compound	N°	Conf. 4	Conf. 5	R	IC_{50} (nM) CCK_1	CCK_2	Selectivity CCK_1/CCK_2	Ref.
	LY288513 (120)	*S*	*R*	4-Br	20,500[a]	19[b]	1,080	248
	LY294920 (121)	*R*	*S*	3-CF_3 4-Cl	17[a]	1,900[b]	0.009	248
	N°			R				
	SC-50,998 (122)				16[c]	>10,000[d]	<0.002	255
	123				18.5[c]	4,800[d]	0.0038	255
	N°	R^1		R^2				
	124	H		H	823[e]	16[f]	51	256
	125	3-F		H	1,000[e]	31[f]	32	256
	126	H		2-CH_3	580[e]	7.8[f]	74	256
	127	H		2-CH_2CH_3	810[e]	25[f]	32	256

[a]Inhibition of the [^{3}H]L-364,718 binding to mouse brain.
[b]Inhibition of the [^{125}I]CCK-8 binding to mouse brain.
[c]Evaluated in rat pancreatic membranes.
[d]Evaluated in guinea pig brain cortex.
[e]Inhibition of the [^{125}I]CCK-8 binding to guinea pig pancreas.
[f]Inhibition of the [^{125}I]CCK-8 binding to guinea pig cortex.

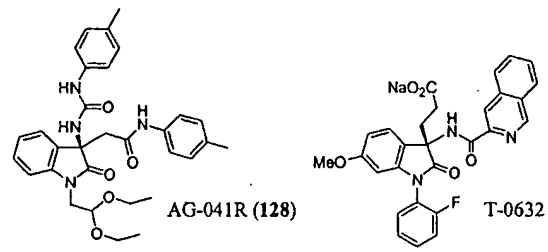
contraction of guinea pig ileal smooth muscle. By intraperitoneal and oral administration, this compound reversed the CCK-8-induced delayed gastric emptying in rats.[255]

The hexahydroazepin-2-one ring, with a similar pattern of substituents to that used in the pyrazolidinone derivatives, was used at Pfizer as an alternative to the benzodiazepine nucleus.[256] This approach led to some compounds with nanomolar affinity at CCK_2 receptors, such as **126**. However, no functional or pharmacological activity of these compounds have been reported.

K. Indol-2-one-Based CCK Antagonists

The 1,3,3-trisubstituted indol-2-one derivatives AG-041R (Table XVII, **128**) and T-0632 (**129**) were selected as selective CCK_2 and CCK_1 receptor antagonists, respectively, from random screening programs. AG-041R (**128**) inhibited pentagastrin-stimulated acid secretion by i.v. administration (ID_{50} = 5 nM/kg) and had no inhibitory effect on carbachol or histamine-stimulated secretion.[257] This antagonist exhibited greater potency than L-365,260 in the water-immersion stress (600-fold) and indomethacin-induced ulcer (6-fold) models.[258] AG-041R dose-dependently inhibited the gastrin-induced histidine decarboxylase activation in intact fasted rats with a ID_{50} value of 0.01 μmol/kg i.v., 5-fold lower that that of the benzodiazepine derivative YF476.[231] This activity has also been studied in enterochromaffin-like (ECL) carcinoma tumors in *Mastomys natalensis* rats both *in vitro* and *in vivo*, where AG-041R also inhibited the histidine decarboxylase gene expression in ECL carcinoid tumor cells and the gastrin-induced DNA synthesis and *c-fos* gene expression.[259]

Table XVII. Indol-2-One-Based CCK Antagonists


AG-041R (**128**)

T-0632 (**129**)

Compound	Affinity CCK$_1$	Affinity CCK$_2$	Selectivity CCK$_1$/CCK$_2$	Reference
AG-041R (**128**)	555[a]	1.11[b]	500	83
T-0632 (**129**)	0.24[c]	5,600[d]	4×10^{-5}	263

[a] IC_{50} (nM) value of inhibition of the binding of [^{125}I]CCK-8 to guinea pig pancreas.
[b] IC_{50} (nM) value of inhibition of the binding of [^{125}I]gastrin to guinea pig gastric glands.
[c] K_i (nM) value of inhibition of the binding of [^{125}I]CCK-8 to rat pancreas.
[d] K_i (nM) value of inhibition of the binding of [^{125}I]CCK-8 to guinea pig cortex.

Additionally, AG-041R induced systemic cartilage hyperplasia by stimulation of chondrocyte proliferation and metabolism, an intrinsic property of this compound no related with its CCK$_2$ receptor antagonism.[260,261] AG-041R also stimulated the repair of osteochondrial defects in a rabbit model.[262] These findings suggest that this compound could be a therapeutic agent for cartilage disorders.

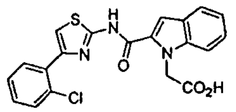
As shown in Table XVII, T-0632 (**129**) is a potent and highly selective CCK$_1$ receptor antagonist, which inhibited the CCK-8-stimulated amylase release from rat pancreatic acini in a concentration-dependent manner with an IC_{50} value of 5.0 nM. This compound also competitively inhibited the CCK-8-induced contraction of the rabbit gall bladder smooth muscle with a pA_2 value of 8.5.[263] In rats, by intravenous and intraduodenal routes, T-0632 dose-dependently inhibited the CCK-8-stimulated pancreatic secretion with ED_{50} values of 0.025 and 0.040 mg/kg, respectively. In mice, orally administered, T-0632 prevented the caerulein-induced pancreatitis, the CCK-8-induced inhibition of gastric emptying, and the CCK-8-induced gall bladder emptying in a dose-dependent manner with ED_{50} values of 0.028, 0.04, and 0.12 mg/kg, respectively. In dogs T-0632 inhibited CCK-8-stimulated pancreatic amylase secretion at a dose of 0.01 mg/kg. In this study, the effects of this CCK$_1$ antagonist were more selective for the pancreas than for the gall bladder.[264] In different models of experimental acute pancreatitis, T-0632 has shown preventive effects by oral or intraduodenal administration,[265,266] and has been studied in Phase I clinical trials for the treatment of pancreatic disorders, although results of these studies have not been reported.

L. Other CCK Antagonists

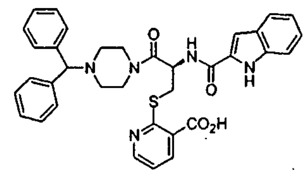
1. Lintitript (SR-27,897)

The CCK$_1$ selective antagonist SR-27,897 (also designed with the generic name of Lintitript, compound **130** of Table XVIII) was obtained by optimisation of a lead compound discovered through random screening of a large chemical library at Sanofi.[267] This compound competitively inhibited the CCK-8-stimulated amylase release in isolated rat pancreatic acini ($pA_2 = 7.50$) and the CCK-8-induced guinea pig bladder contractions ($pA_2 = 9.57$). This antagonistic activity was confirmed in *in vivo* gastrointestinal models. Thus, at 1 mg/kg (i.v.) it completely reversed the CCK-induced amylase secretion in rats, and 3 μg/kg (p.o.) antagonized by 50% the CCK-induced inhibition of gastric emptying in mice, and inhibited the CCK-induced gall bladder emptying in mice with a ED_{50}

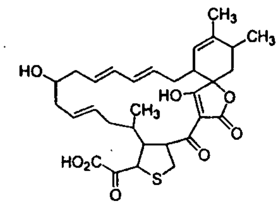
Table XVIII. Miscellaneous Structure CCK Antagonists



SR-27,897
(Lintitrip, **130**)



TP-680 (**131**)



Tetronothiodin (**132**)

Compound	Affinity CCK$_1$	Affinity CCK$_2$	Selectivity CCK$_2$/CCK$_1$	Reference
SR-27,897 (130) (Lintitript)	0.58^a	489^b	843	267
TP-680 (131)	1.2^c	1,812^d	1,510	278
Tetronothiodin (132)	>100,000^a	3.6^e	<4×10^{-5}	280

^{a}IC$_{50}$ (nM) value of inhibition of the binding of [^{125}I]CCK-8 to rat pancreas.
^{b}IC$_{50}$ (nM) value of inhibition of the binding of [^{125}I]CCK-8 to guinea pig cortex.
^{c}K_i (nM) value of inhibition of the binding of [^{125}I]CCK-8 to rat pancreas.
^{d}K_i (nM) value of inhibition of the binding of [^{125}I]CCK-8 to rat cerebral cortex.
^{e}IC$_{50}$ (nM) value of inhibition of the binding of [^{125}I]CCK-8 to rat cerebral cortex.

value of 27 μg/kg (p.o.). SR-27,897 showed a long-lasting action in all the experiments, with no differences between oral and intravenous routes of administration. In comparison with devazepide, SR-27,897 increased the gall bladder volume of fasting mice, but its effect was 10-fold lower than that of devazepide.[267] SR-27,897 dose-dependently antagonized the CCK-8-induced hypophagia and hypolocomotion in rats, two behavioural effects associated with the stimulation of CCK$_1$ receptors, with ED$_{50}$ values of 0.003 and 0.002 mg/kg (i.p.), respectively, while devazepide in the same tests showed ED$_{50}$ values of 0.02 and 0.1 mg/kg (i.p.), respectively. In these tests the i.p./p.o. ratio for SR-27,897 was near unity, suggesting a high oral bioavailability.[268] SR-27,897 inhibited the preprandial pancreatic secretion and greatly reduced the postprandial pancreatic juice and enzyme outflows in milk-fed calves, demonstrating the implication of CCK and CCK$_1$ receptors in mediating the postfeeding pancreatic response.[269] Similarly, the inhibitory effect of SR-27,897 on the CCK-8-induced contraction of human lower oesophageal sphincter strips demonstrated that the contractile effect of CCK is mainly due to the activation of CCK$_1$ receptors.[270] SR-27,897 also inhibited the pressor effects of CCK on blood pressure and reversed the bradycardic responses to tachycardia in conscious rats, providing evidence for the involvement of CCK$_1$ receptors in cardiovascular regulation.[271] On the other hand, neither SR-27,897 nor devazepide exhibited anxiolytic-like effects in the elevated zero-maze test in rats, while the CCK$_2$ antagonists L-365,260 and PD-135,158 both had significant anxiolytic activity in this assay.[272] In Phase II clinical studies, SR-27,897 accelerated gastric emptying of solids, while gastric emptying of liquids was not significantly altered by oral administration in healthy male volunteers. Moreover, this CCK$_1$ antagonist markedly increased postprandial plasma CCK release, while distinctly reduced postprandial pancreatic polypeptide.[273] Several receptor mutagenesis studies have shown that SR-27,897 occupies different binding sites from its analogue CCK$_1$ agonist SR-146,131 and CCK-8 at the CCK$_1$ receptor.[274–277]

2. TP-680

The selective CCK$_1$ receptor antagonist TP-680 (Table XVIII, **131**) was also the result of a random screening program. This antagonist was approximately 17-fold less potent than devazepide, but 106-

fold more potent than loxiglumide in inhibiting the CCK-8-stimulated amylase release from rat pancreatic acini.[278] TP-680 by intravenous administration in mice has shown long-lasting antagonistic properties on CCK-8-stimulated pancreatic secretion, gastric emptying, and gall bladder contraction. The selectivity for these activities was gastric emptying > pancreatic secretion > gall bladder contraction.[279]

3. *Tetronothiodin*

The highly selective CCK_2 antagonist tetronothiodin (**132**) was isolated from the fermentation broth of *Streptomices sp.* NR0489.[280,281] This compound inhibited the CCK-8 binding to rat cerebral cortex membranes with nanmolar binding affinity, whereas it did not showed affinity at rat pancreatic membranes. It also inhibited the CCK-8-induced Ca^{2+} mobilization in rat anterior pituitary cells GH3, but it did not inhibit the basal cytosolic Ca^{2+} concentration.[280]

4. CONCLUSIONS AND FUTURE PERSPECTIVES

Over the past 15 years, the search of CCK receptor ligands has evolved from the initial CCK structure derived peptides towards peptidomimetic or non-peptide agonists and antagonists with improved pharmacokinetic profile. This research has provided a broad assortment of potent and highly selective antagonists for both CCK receptor subtypes, CCK_1 and CCK_2, of diverse chemical structure. These antagonists, as pharmacological tools, have highly contributed to the characterization and localization of CCK receptor subtypes, as well as to the study of physiological and pathological actions of CCK. However, despite the progress in this field, the complex biological effects of CCK mediated by CCK_1 and CCK_2 receptors are not yet completely established. Particularly, additional research is necessary for gaining insight into the complex system of interaction of CCK with other neurotransmitters both in the CNS and in the periphery. Pharmacological research is also necessary to confirm that the different binding affinities determined for some antagonists by using different radioligands, and in some cases the discrepancies observed between binding potency and antagonistic potency, are due to the existence of different binding states and not to receptor subtype hetereogeneity. This research will help to characterize the different binding states for each receptor subtype as well as the biological actions mediated by their activation. Furthermore, at the molecular level, as in the case of other G-protein coupled receptors, the growing studies focused on the characterization of agonists and antagonists binding domains at both CCK_1 and CCK_2 receptors, would contribute to a better knowledge of the complex dynamic equilibrium in the receptor activation–inactivation process and their related biological responses. Additionally, these molecular studies will foster the *de novo* receptor structure-based design of new selective and more effective antagonists.

Concerning the therapeutic potential of CCK antagonists, although several CCK_1 and CCK_2 receptor antagonists, summarized in Table XIX, have reached different phases of clinical trials, the complex interconnected physiological actions of CCK have hampered their clinical development. On one hand, CCK_1 antagonists entered development mainly for the treatment of pancreatic disorders and as prokinetics for the treatment gastroesophageal reflux disease, bowel disorders (e.g., irritable bowel syndrome), and gastroparesis. Their potential in the treatment of pancreatitis and pancreatic cancer is showing particular promise. However, their therapeutic development has been hampered by the side effect of stone growth in the gall bladder, which was firstly reported from the clinical trial of devazepide (**19**). Conversely, this side effect has not been reported for loxiglumide (**7**), the most advanced CCK_1 antagonist in clinical studies for the treatment of acute pancreatitis, or for lintitript (**130**). If this side effect were confirmed as a general property related to the CCK_1 receptor antagonism, those antagonists as T-0632 (**129**) which are more selective for the pancreas than for the gall bladder would have some advantage.

Table XIX. Summary of CCK Antagonists That Have Reached Clinical Trials

Compound	*Receptor subtype selectivity*	*Highest clinical phase*[a]	*Indication*
Proglumide (3)	Non-selective	Marketed	Antiulcer
Loxiglumide (7)	CCK_1	Pre-registered	pancreatitis
Dexloxiglumide (8)	CCK_1	Phase III	Irritable bowel syndrome
KSG-504 (11)	CCK_1	Phase I	Pancreatic disorders
2-NAP (12)	CCK_1	Phase I	Pancreatic disorders
Spiroglumide (13)	CCK_2	Phase II	Gastric secretion disorders
Itriglumide (17)	CCK_2	Phase I	Anxiolytic, antiulcer
Devazepide (18)	CCK_1	Phase II (discontinued)	Gastric motility disorders
		Phase II	Pain
Pranazepide (20)	CCK_1	Phase II	Pancreatic disorders
Tarazepide (21)	CCK_1	Phase II	Gastric emptying disorders
L-365,260 (22)	CCK_2	Phase II (discontinued)	Anxiety, drug dependence
		Phase II	Pain
YM022 (30)	CCK_2	Phase I	Gastric secretion disorders
YF476 (31)	CCK_2	Phase I	Gastro-oesophagal reflux
GV150013X (41)	CCK_2	Phase II	Anxiety disorders
		Phase II	Sleep disorders
S-0509 (49)	CCK_2	Phase I	Gastric secretion disorders
CI-988 (58)	CCK_2	Phase II	Anxiety and panic disorders
T-0632 (129)	CCK_1	Phase I	Pancreatic disorders
Lintitript (130)	CCK_1	Phase II	Pancreatic cancer therapy, eating disorders

[a]Information from the Ensemble Data Base of Prous Science.

On the other hand, CCK_2 antagonists have been entered development mainly for the treatment of gastric acid secretion and anxiety disorders. Although CCK_2 receptor antagonists represent an alternative therapeutic approach for the treatment of peptic ulcer and gastric acid secretion disorders, the clinical results of L-365,260 (**22**) and spiroglumide (**13**) are not encouraging as relatively high doses were required to obtain results equivalents to those of the H_2-receptor antagonist famotidine or the proton pump inhibitor omeprazole. The effectiveness of the current treatments of duodenal ulcer patients through the use of these H_2-receptor antagonists or proton pump inhibitors supplemented by *H. pylori* eradication has diminished the therapeutic opportunity for CCK_2 antagonists in the therapy of gastric acid-related diseases. However, the therapeutic potential of these antagonists will be fully evaluated only when the results of the in-progress clinical trials of the second generation CCK_2 antagonists, with improved oral bioavailability, such as itriglumide (**17**) and YF476 (**30**), are available. Concerning this issue, it is important to note that, in *in vivo* animal models, itriglumide was effective in prevention of gastric damage and YF476 reversed the hypergastrinemia and cell proliferation caused by omeprazole in the gastric mucosa.

The discovery of the panicogenic effect of CCK-4 in man raised the hypothesis of the involvement of CCK_2 receptors in the pathogenesis of panic disorders, consequently CCK_2 antagonists were considered potential anxiolytic agents. In fact, most of the potent CCK_2 antagonists have shown anxiolytic-like effects in diverse animal models, without the side effects of the classic benzodiazepine anxiolytics, such as sedation, development of tolerance, and withdrawal anxiogenesis after termination of the treatment. However, these anxiolytic effects have not been confirmed in clinical trials neither in patients with generalized anxiety and panic disorders neither against CCK-4-induced panic symptoms in healthy volunteers. These discouraging clinical results have been attributed to the poor bioavailability and blood–brain permeability of the first generation CCK_2 antagonists studied [L-365,260 (**22**) and CI-988 (**58**)], and it has been suggested that the second generation antagonists with improved oral bioavailability might give more encouraging results.

Nevertheless, there are doubts about the actual role of CCK_2 receptors in anxiogenesis.[11] Regarding this issue, it is noteworthy that recent studies have shown that CCK_2 receptor-deficient mice did not show behavioral modifications compared to wild-type mice in the elevated plus maze test of anxiety and in the motility conditioned suppression test, indicating that compensatory mechanisms very likely occur following CCK_2 receptor inactivation.[282] Therefore, considerable pharmacological work is still needed to really assess the therapeutic potential of both CCK_1 and CCK_2 receptor antagonists.

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